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ORIGINAL ARTICLES

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Characterization of Suicide, Suicidal Ideation, and Self-harm Attempts: A Pre-hospital Descriptive Study

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Abstract

Objective: This study aimed to characterize demographic and socioeconomic data, on-scene medical conditions, methods used, and emergency medical systems (EMS) response times and distances for patients and individuals seeking help from EMS due to suicidal ideation, self-harm, and suicide attempts.

Methods: This retrospective, cross-sectional, and descriptive study. The study includes patients and individuals in Manisa who were attended by EMS providers following calls to the 112 emergency call center for suicidal ideation, self-harm, and suicide attempts over two years (2022-2023).

Results: The study included 875 cases in 2022 (51.2%) and 835 in 2023. It was observed that the incidents were more common among young individuals (average age 29), males (55%), the unemployed (82.9%), those living in urban areas (77.7%), on Mondays (15.8%), and between 17:00 and 00:00 (41.8%). Most patients were transported to the hospital by EMS providers (88%). High rates of alcohol consumption (29.3%) and aggressive behaviors (17.9%) were noted. The most common method of suicide attempt was drug overdose (53.7%), particularly with antipsychotics (36.8%) and paracetamol (31.4%). Suicide attempts using the patient's own medication were frequent (34.7%). For those who self-harmed with sharp objects, the most commonly injured areas were the hand and wrist (41.1%) and forearm (35%). The average response times for the EMS to reach the scene were 391.5 s in urban areas and 875 s in rural areas.

Conclusion: Young males, unemployed individuals, and those living in urban areas were the most common patients and individuals attended by EMS providers. The most common method of suicide attempt was high-dose drug ingestion, particularly antipsychotics and paracetamol. The highest on-scene fatality rates were observed with hanging and firearm use, whereas sharp object injuries were frequent but had lower on-scene fatality rates. Additionally, response times and distances were longer in rural areas.

Keywords: Emergency medical systems, suicide, suicidal ideation, self-harm

INTRODUCTION

Suicidal ideation encompasses a wide range of thoughts, wishes, and preoccupations related to death and suicide. Non-fatal self-injury without suicidal intent is categorized as deliberate self-harm, whereas self-injury with the intent to die, resulting in non-fatal injury, is defined as a suicide attempt. Self-harm that results in death is also classified as suicide (1,2). Although definitions are often confused, they signify important differences in outcomes. Every suicide is a tragedy with far-reaching impacts on families, communities, and nations, leaving lasting effects on those left behind.

The World Health Organization (WHO) data on suicide epidemiology revealed that over 700,000 people die by suicide annually; in 1998, suicide accounted for 1.8% of the global disease burden, which is projected to rise to 2.4% by 2020. In 2019, suicide was ranked as the fourth leading cause of death among 15-29-year-olds worldwide, with 77% of suicides occurring in low- and middle-income countries (3,4). Approximately 20%

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of global suicides are due to pesticide self-poisoning in rural agricultural regions of low- and middle-income countries, with the use of hanging and firearms as common methods (5).

Addressing suicide requires multifaceted strategies at both national and international levels (6). A key strategy involves the organized activation of healthcare systems following incidents of self-harm or suicide attempts. Effective management of the injured or patients is critical to prevent suicidal thoughts and attempts to result in death and to avert acute and chronic health conditions. It is crucial to protect individuals who have attempted suicide and to protect society from the potential risks associated with such individuals. First responders, including law enforcement officers, firefighters, emergency medical systems (EMS) clinicians, and public safety telecommunication officers, play a vital role in ensuring public safety and health. EMS providers, who are often the first callers during suicide attempts, have a strategic position in suicide prevention (7).

Nonetheless, there is limited guidance for EMS providers regarding managing suicidal patients, ensuring scene safety, and protecting the community (8). Given the methods used in suicide attempts (e.g., poisoning, hanging, drowning, firearms, explosives, and jumping from heights), if these attempts do not result in death, early and rational intervention can prevent fatalities. EMS providers are pivotal in managing acute-phase complications (8). To enable effective intervention, it is essential to accurately identify this patient group at the national level and to define recent suicide attempts and suicides, thereby guiding national and international strategies.

In Turkey, research focusing on the pre-hospital management and the profiling of this patient group is limited (9). This study aimed to characterize patients and victims who contacted the emergency call center (112) due to suicidal thoughts, self-harm, or suicide attempts and were attended by EMS providers.

METHODS

Study Design and Setting

This retrospective, descriptive, and cross-sectional study was conducted in Manisa, Turkey. This category includes patients and individuals who were attended by EMS providers following calls to the 112 emergency call center for suicidal ideation, self-harm, and suicide attempts over a two-year period (2022-2023). Preliminary research permission was obtained from the Provincial Health Directorate of Manisa Governorate of the Republic of Turkey (permission was obtained on March 11, 2024, decision number: E79593712-238808379). The study protocol was reviewed and approved by the İzmir Provincial Directorate of Health University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (İzmir/Turkey) Non-Interventional Clinical Research Ethics Committee (decision number: 2024/03-26, date: 03.04.2024). Patient consent was not obtained due to the retrospective nature of the study.

Participants

The study population comprised patients and individuals in Manisa, Turkey, who received EMS intervention following calls to the 112 emergency call center for suicidal ideation, self-harm, and suicide attempts in 2022 and 2023. In 2023, EMS providers responded to 1,163 calls, and in 2022, they responded to 1,132 calls for these reasons. False alarms were excluded from the study. Data on these cases were entered electronically into the Manisa 112 chief physician's office patient and injury identification system by EMS providers and verified by 112 team leaders.

Data Collection

The study utilized international classification of diseases-10 codes ranging from X60 to X849, which were electronically entered by EMS providers into the Manisa 112 chief physician's office patient and injury identification system. The methods were categorized into seven groups: pesticide or unspecified poisoning (X68-X699), other poisoning drugs (X60-X679), hanging (X70-X709), drowning (X71-X719), firearms and explosives (X72-X759), jumping from height (X80-X809), and other methods including corrosive substances (10). The research data were verified and completed by cross-referencing the electronic records with the paper documents provided by the EMS providers. Patients and individuals with incomplete electronic and paper records were excluded from the study. Data entry was performed by a paramedic and a secretary, and it was subsequently verified by a general practitioner working in EMS.

Alcohol consumption was recorded based on EMS provider reports as either present or absent; no invasive tests were conducted. The status of the patients' consciousness, pupils, respiration, skin, and pulse were recorded in the electronic system using descriptive terms rather than numerical values, which were then evaluated. Vital signs measured and recorded in the scene were included in the study via an electronic system. However, the vital signs of patients declared dead at the scene were not included in the analysis.

Patients who self-injured with sharp objects were classified according to anatomical regions: hand-wrist, forearm, humerus, head-face, neck, thorax, abdomen, pelvis, lower extremity, genital area, and multiple regions. Patients with a history of sharp object consumption were classified under abdominal injuries.

Response time, station response, transport time, intervention time, hospital arrival time, and time spent were measured by the system based on ambulance responses. Special circumstances (e.g., ambulance breakdowns, accidents) were excluded from the study. Additionally, the distance to the incident and the distance between the incident and hospital were recorded from the electronic system containing the ambulance data.

Statistical Analysis

The statistical analysis was conducted using SPSS software (version 29, IBM Corp., Armonk, NY). Descriptive statistics summarize the data, with counts and percentages for categorical variables, and mean ± standard deviation or median [interquartile range (IQR) 25^{th}-75^{th}] for continuous variables. The assumption of normal distribution for the groups was evaluated by visually inspecting histograms and performing the Shapiro-Wilk test.

RESULTS

A total of 1,710 patients were included in the study. In 2022, there were 875 cases (51.2%) and 835 cases in 2023. Table 1 presents the demographic characteristics of the patients. The median age of the patients was 29 years (IQR 21-40), and 45% of the patients were female (n=770). The vast majority of the patients were Turkish citizens (98.5%, n=1,684), and 4.4% of the patients had no health insurance (n=76). Additionally, 3.8% of the patients were incarcerated (n=65), and 82.9% were unemployed (n=1,418). Only 3.2% of patients were retired (n=55), and 22.3% were from rural areas (n=381). The most frequent day for cases was Monday (15.8%, n=270), while Friday had the fewest cases (13.6%, n=232). Most calls were made between 17:00 and 00:00 (41.8%, n=715).

Table 1. Distribution of cases by demographic characteristics and time

Categories	Variables	Total (n=1,710)
Demographic data	Age (in years)	29 (21-40)
	Sex (female)	45% (770)
	Nationality (Turkish)	98.5% (1,684)
Socioeconomic data	Uninsured	4.4% (76)
	Incarceration	3.8% (65)
	Unemployed	82.9% (1,418)
	Retired	3.2% (55)
	Rural	22.3% (381)
Days of the week	Monday	15.8% (270)
	Tuesday	13.9% (238)
	Wednesday	13.9% (238)
	Thursday	14.2% (242)
	Friday	13.6% (232)
	Saturday	14.4% (247)
	Sunday	14.2% (243)
Time of day	08:00-17:00	31.5% (538)
	17:00-00:00	41.8% (715)
	00:00-08:00	26.7% (457)

Information about the patients' medical conditions at the scene is provided in Table 2. The mean systolic blood pressure was 120.4±26.6 mmHg, and the mean diastolic blood pressure was 73.9±16.4 mmHg. The median peripheral oxygen saturation was 98% (IQR 98-99), and the mean pulse rate was 92.3±24.8. Alcohol intoxication was present in 29.3% of the patients (n=501). Aggressive behavior was observed in 17.9% of the patients (n=306). Black triage was assigned to 4.9% of the patients (n=83), while green triage was assigned to only 5.3% (n=90). Most patients were alert (81.4%, n=1,392), while 12.6% (n=216) were unresponsive. History of psychiatric diagnosis was present in 18.3% of the patients (n=313). Most cases were transported to the hospital (88%, n=1,505); 7% (n=120) were declared dead in the scene.

The most common method of suicide attempt was drug ingestion (53.7%, n=918) (see Table 3 for mortality rates), with 0.7% (n=12)

Table 2. Medical characteristics recorded by EMS at the scene

Categories	Variables	Total (n=1,710)
Vitals	Systolic BP (mmHg)	120.4±26.6
	Diastolic BP (mmHg)	73.9±16.4
	SpO_2	98 (98-99)
	Pulse rate (/minutes)	92.3±24.8
Level of consciousness	Alert	81.4% (1,392)
	Verbal	4% (69)
	Pain	1.9% (33)
	Unresponsive	12.6% (216)
Triage	Green	5.3% (90)
	Yellow	48.3% (826)
	Red	41.5% (711)
	Black	4.9% (83)
Additional parameters	History of psychiatric diagnosis	18.3% (313)
	Under alcohol	29.3% (501)
	Aggressive behavior	17.9% (306)
Outcome	Refusal of care	5% (85)
	DOA	7% (120)
	Transfer	88% (1,505)

BP: Blood pressure, SpO_2: Saturation of peripheral oxygen, DOA: Deceased on arrival, EMS: Emergency medical systems

attempting multiple methods. Among those who attempted suicide by drug ingestion (n=918), psychotropic drugs were the most common (36.8%, n=338), followed by paracetamol (31.4%, n=288) (Table 4). Multiple drug ingestion was observed in 19.1% of the patients (n=175), and 34.7% used their own medication for the suicide attempt. Self-harm with sharp objects was observed in 23% of the patients (n=394). The most frequently injured anatomical region was the hand-wrist area (41.1%, n=162) (Table 4). Multiple regions were injured in 15.2% of the patients (n=60).

Figure 1 presents ambulance data based on rural and urban conditions. The median command response time was 55 s (IQR 35-82), and the median station response time was 41 s (IQR 22-60). The median time to reach the scene after the call was 391.5 seconds (IQR 295-583). The median time for ambulance crews to provide on-scene care was 577 s (IQR 368.75-881), and the median time to transport the patient to the hospital after intervention was 600 s (IQR 420-776.5). The median time ambulances were occupied by these interventions and hospital transport was 2091.5 s (IQR 1620-2934.5). The median distance the ambulances traveled to reach the scene was 2 km (IQR 1-4), and the median distance from the scene to the hospital was 3 km (IQR 2-5).

DISCUSSION

To prevent successful suicide attempts, developing regional intervention activation plans tailored to the specific conditions of each region and preparing readiness plans based on these data (6,11). Timely access to information on local epidemiological trends is crucial for community-specific suicide prevention efforts (12). Therefore, this study compared regional epidemiological and demographic data with national and international figures. The mean age of individuals receiving EMS services for suicidal ideation and attempts was 29 years. According to United States Centers for Disease Control and Prevention (CDC) data, adults aged 35-64 account for 46.8% of all suicides in the United States, where suicide is the 8th leading cause of death for this age group (13). A 2019 WHO report highlighted suicide as a global phenomenon and the fourth leading cause of death among those aged 15-29 worldwide (5). Our findings align more closely with the WHO data than CDC figures, suggesting that the WHO's global data may be more consistent with our regional epidemiological data.

Gender is another important demographic factor (14). Although studies often report higher rates of suicidal behavior among females, our research found a higher incidence among males, consistent with other studies (15,16). This discrepancy is particularly notable in studies including both rural and urban populations, in which a higher incidence of suicide attempts among males has been observed (17). Socioeconomic factors such as urbanization, employment status, and health insurance are linked to suicide patterns (18). Our study also evaluated factors such as nationality, lack of health insurance, imprisonment, unemployment, retirement status, and rural living. While unemployment and lack of health insurance were consistent with the literature, a notable finding was the higher incidence of EMS calls for suicidal ideation and self-harm in urban areas than in rural areas.

CDC data suggest significant geographic variations in suicide rates, with higher rates observed in rural areas with lower

Table 3. Methods of suicide attempts and associated mortality rates

Method	Total (n=1,710)	Mortality
Pesticide	3.6% (62)	1.6% (1)
Drug	53.7% (918)	0.3% (3)
Hanging	7.3% (124)	58.1% (72)
Drowning	0.2% (4)	25% (1)
Firearm injury	3.3% (57)	57.9% (33)
Jumping from a height	6% (103)	5.8% (6)
Sharp object injuries	23% (394)	1% (4)
Corrosive substances	3.2% (54)	0% (0)
Multiple methods	0.7% (12)	0% (0)

Table 4. Distribution of drug overdoses and self-harm with sharp objects by region

Drug types	Total (n=918)	Regions of sharp object injuries	Total (n=394)
Paracetamol	31.4% (288)	Hand-wrist	41.1% (162)
Anticoagulant/ antiplatelet	3.4% (31)	Forearm	35% (138)
Anticonvulsant	6.3% (58)	Humerus	14.2% (56)
Antipsychotics	36.8% (338)	Head-face	6.9% (27)
NSAID	18.7% (172)	Neck	8.4% (33)
Herbal	5.6% (51)	Thorax	3% (12)
Methanol	2.6% (24)	Abdomen	3.6% (14)
Antihypertensive	3.4% (31)	Pelvis	1% (4)
Antidiabetic	1.5% (14)	Lower extremity	4.1% (16)
Psychotropics	12.7% (117)	Genital	0.8% (3)
Multiple drug groups	19.1% (175)	Multiple regions	15.2% (60)
Suicide using own medication	34.7% (319)		

NSAID: Non-steroidal anti-inflammatory drug

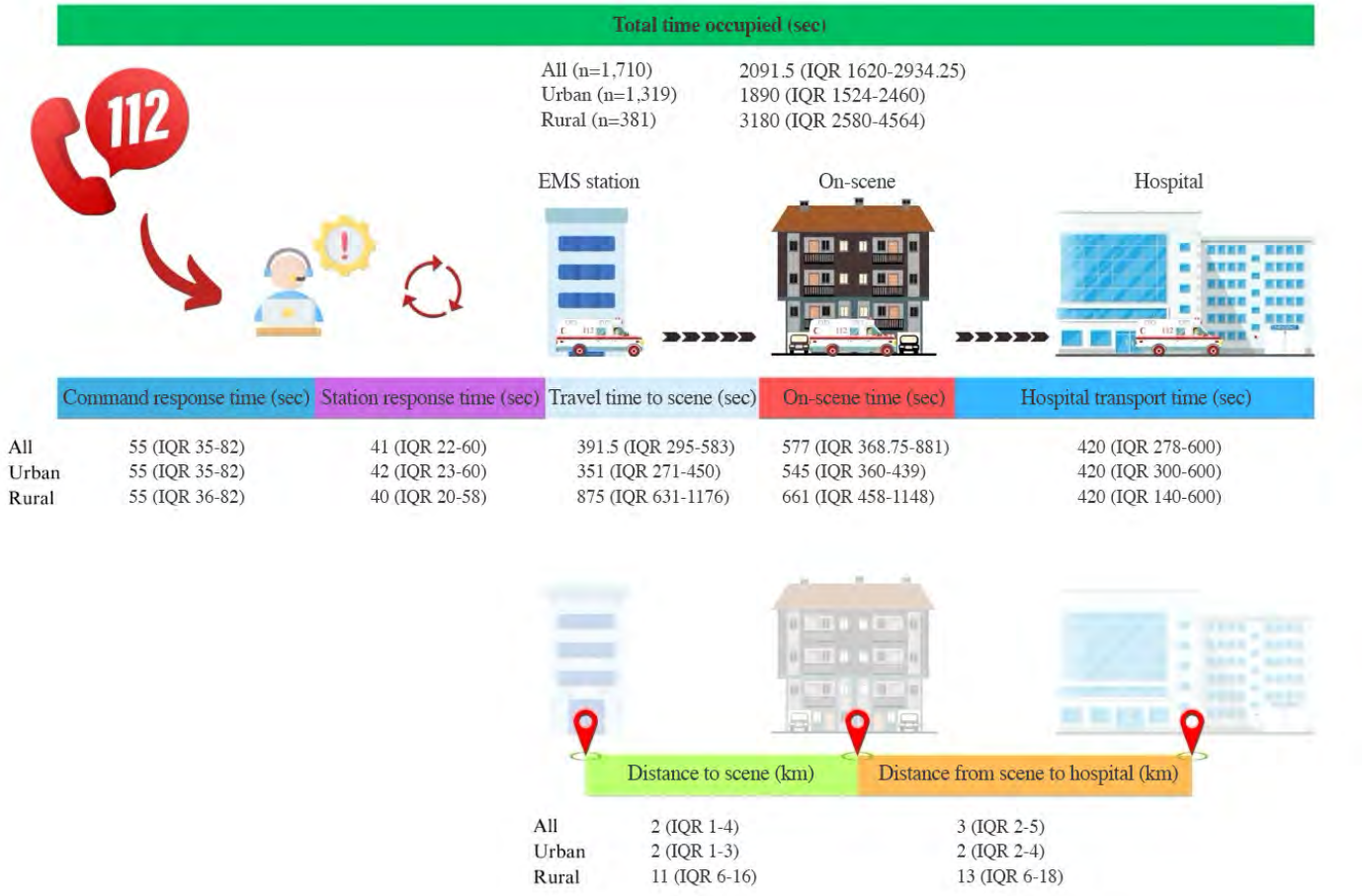

Figure 1. Ambulance response and transport metrics
IQR: Interquartile range, EMS: Emergency medical systems, sec: Seconds, km: Kilometers

population densities (13,17). However, our study found a higher frequency of urban EMS calls, which is noteworthy.

Individual-level interventions are critical for preventing suicide attempts when suicidal thoughts emerge (19). This study identified the most frequent times for suicidal ideation, attempts, and completed suicides, which occurred most commonly on Mondays and between 17:00 and 00:00. This time frame is significant because it falls outside regular working hours. Although EMS systems and emergency services operate 24/7 in Turkey and many other countries, the availability of necessary units for treating and intervening during these hours is limited. Regional plans for areas with frequent suicidal ideation, attempts, and suicides should emphasize readiness during these time slots.

Three critical conditions were observed in the EMS evaluation in the scene. First, 18.3% of patients had a psychiatric diagnosis. Patients with psychiatric diagnoses have a higher likelihood of attempting suicide (20). These patients are a crucial target group for prevention efforts given their previous diagnosis. Furthermore, the specialization of EMS services for such interventions, based on the regional psychiatric disease burden, could be a strategic choice.

Second, 29.3% of patients had consumed alcohol. The WHO reports a causal relationship between harmful alcohol use and a range of mental and behavioral disorders, other non-communicable conditions, and injuries (21). Similarly, our study found a high incidence of alcohol use among patients. Combating alcohol use is an essential element of suicide prevention plans.

Third, 17.9% of patients exhibited aggressive behavior. Managing patients with suicidal ideation, attempts, and completed suicides by EMS is challenging because of the need for early intervention in unique conditions where safety is not yet ensured (22). Therefore, the high potential for aggression among patients highlights the need for law enforcement involvement, scene safety protocols, and specialized training for EMS personnel.

In our study, the most common method of suicide attempt was drug ingestion, followed by sharp object injuries, hanging, and jumping from a height, while the least common were drowning, corrosive substance use, firearm use, and pesticide use. The highest success rate of on-scene deaths was observed with hanging and firearms. These findings align with the literature regarding the mortality rates of hanging and firearm use, and the lower incidence of drowning can be attributed to the non-coastal nature of the study area (23).

Preventive measures against individual firearm ownership could further reduce the use of firearms in such acts. Among patients who used drugs for suicide attempts, antipsychotic drugs and paracetamol were the most common, with 34.7% of the patients using their own medication. These data align with the finding that suicide risk is highest within the first year after initial hospitalization for first-episode psychosis and shortly after discharge for general psychiatric inpatients (24). Patients in treatment and likely to possess antipsychotic medications at home represent a significant risk group. This underscores the importance of protecting and monitoring these patients, with roles for both family members and healthcare providers in identifying the agents used in suicide attempts. Due to its widespread use as an analgesic and antipyretic, paracetamol frequently appears in overdose-related suicide attempts globally (25). Similarly, in our study, paracetamol was one of the most commonly used drugs for self-harm and suicide attempts.

Self-harm with sharp objects was prevalent although the success rate of on-scene deaths was lower. Consistent with the literature, upper extremity cuts were the most frequent (26). EMS providers play a crucial role in managing these patients, as the key factor determining their survival is the management of hypovolemic shock at the scene and during pre-hospital care (27). Early intervention and rational treatment approaches are expected to yield positive outcomes. However, the high rates of aggression observed in our study highlight the significant risk posed to EMS providers, especially when patients who have self-harmed with sharp objects still possess their instruments. This concern also applies to patients who use firearms for suicide attempts or management. Given these data, the potential harm these patients pose to EMS providers must be considered, and interventions should be multidisciplinary, involving regional law enforcement to ensure scene safety.

Lastly, descriptive data in this study include the reaction times and distances covered by EMS providers after receiving 112 calls. The study found a higher frequency of calls from urban areas than rural areas. Additionally, although command and station response times were similar in rural and urban areas, the travel time to the scene, on-scene intervention time, hospital transport time, total time occupied by EMS personnel, and distances covered from the scene to the hospital were longer in rural areas (28). This finding emphasizes the need for equitable distribution of healthcare resources. Early access and intervention projects for suicide attempt and ideation in rural areas are essential across all communities.

In conclusion, suicidal ideation, self-harm, and suicide form a cycle. Preventing patients from entering this cycle is as crucial as intervening after an attempt. The first medical contact for these patients is often with EMS providers. Successful outcomes are more likely when regional initiatives utilize these experiences to prevent and plan for future attempts.

CONCLUSION

In Manisa, among patients and individuals with suicidal ideation, self-harm, and on-scene suicides attended by EMS, providers, demographic, social, and economic data revealed a higher prevalence of young males, unemployment, and urban living. The most common method of suicide attempt was drug overdose, particularly involving antipsychotics and paracetamol. The highest on-scene fatality rates were observed with hanging and firearms, whereas sharp object injuries were frequent but had lower on-scene fatality rates compared with those with hanging and firearms. Additionally, transportation distances and times were longer in rural areas.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the İzmir Provincial Directorate of Health University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (İzmir/Turkey) Non-Interventional Clinical Research Ethics Committee (decision number: 2024/03-26, date: 03.04.2024).

Informed Consent: Patient consent was not obtained due to the retrospective nature of the study.

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ORIGINAL ARTICLE

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The Relationship of Individuals' Depression and Anxiety Levels with Sociodemographic Characteristics and Worries and Attitudes Towards Outbreak During the COVID-19 Outbreak

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Abstract

Objective: This study aimed to investigate the relationship between depression, anxiety, and stress levels in individuals and sociodemographic characteristics and worries and attitudes towards the pandemic during the coronavirus disease-2019 (COVID-19) outbreak.

Methods: This cross-sectional study was conducted using an online survey. Participants were evaluated using a sociodemographic data form, the COVID-19 worry and attitude questionnaire, the depression anxiety and stress scale (DASS-21), and the impact of event scale-revised (IES-R).

Results: A total of 633 respondents were included in the study. In total, 23.2% (n=122) of respondents rated the psychological impact of the outbreak as moderate or severe (IES-R >33). Moderate, severe, and very severe depression, anxiety, and stress levels were determined in 29.7% (n=188), 19% (n=122), and 13.4% (n=85) of respondents, respectively. Binary logistic regression analysis showed that gender, accompanying chronic disease, employment status, COVID-19 contact history, poor self-rated health status, and worries related to the pandemic were factors significantly associated with the DASS-21 and IES-R scores.

Conclusion: The mental health of individuals was negatively affected by worries about socioeconomic and pandemic-related uncertainties during the COVID-19 pandemic. Social and health policies should be planned to reduce individual concerns during the pandemic.

Keywords: COVID-19, anxiety, depression, stress

INTRODUCTION

Coronavirus disease-2019 (COVID-19) pandemic, which started in Wuhan, China in December 2019, spread globally in a short period. As of 11 March 2020, when the virus was detected in Turkey for the first time, the government implemented several measures, including school closures, stay-at-home orders, and lockdowns. In many countries where the virus has spread, individuals have been warned through health institutions and the media to obey social distancing rules and restrict themselves from social environments. Uncertainty in education, social life, and business life has gradually increased (1).

Under these negative conditions, studies have shown that the rates of anxiety and depression are high among individuals during the pandemic. In a study conducted in China, 53.8% of respondents rated the psychological impact of the outbreak as moderate or severe; 16.5% reporting moderate or severe depression symptoms, 28.8% reporting moderate or severe anxiety symptoms, and 8.1% reporting moderate or severe

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stress symptoms (2). Studies have reported percentages of post-traumatic stress symptoms as 7% and 15.8% (3,4). Several studies have reported risk factors for anxiety and depression. Female gender (2,5,6), urban residence (6), low self-rated health status (2), accompanying chronic disease (5,6), and contact history of suspected or confirmed cases (2) are defined risk factors.

Descriptive studies investigating the concerns of individuals during the pandemic are limited. Concerns are defined as repetitive negative or catastrophic thoughts accompanied by worries about uncertain circumstances (7,8). During the pandemic, individual concerns may be related to health anxiety as well as many other conditions, such as social and economic uncertainty, uncertainties about protection from the virus and treatment, and social restrictions. Concerns can be a factor in mobilizing individuals to deal with potential threats and increase protective behaviors (wearing masks) that can mitigate threats (7,9). However, increased intense worry is associated with increased mental health problems in individuals (8,10). Defining the extent to which individuals are affected by these concerns will help determine the risks of mental illness and take appropriate precautions.

This study aims to investigate pandemic-related worries and their effects on anxiety and depression levels.

METHODS

An online questionnaire was designed to investigate the psychological responses of individuals over the age of 17 living in various provinces of Turkey to the COVID-19 pandemic. The Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee approved the study (approval number: 24237859-379, date: 19.06.2020). After approval, data were collected through an online questionnaire for four weeks. Individuals who read the informed consent form about the study via social media were asked to fill out the questionnaire. Google Docs software was used to collect data. This study was conducted in accordance with the principles of the Helsinki Declaration.

The sociodemographic data form includes age, gender, education level, income level, marital status, with whom he/she lives (living situation), having children, employment status for the last 14 days, direct or indirect contact history with COVID-19, and accompanying chronic disease. In addition, the participants were asked to rate their physical health.

In the COVID-19 worry and attitude questionnaire, participants were asked to rate each statement related to the COVID-19 pandemic (e.g., are you worried about spreading the virus to others? Are you worried about experiencing financial difficulties?). The questionnaire was designed as a 5-point Likert-type feedback survey (0= Never, 4= Almost always). The items of precautionary behaviors in the questionnaire were hand washing/disinfection, wearing a mask, and avoiding close contact. The internal consistency of the survey was found to be good (Cronbach's alpha =0.864).

The depression anxiety and stress scale (DASS-21) was developed by Lovibond and Lovibond (11). This scale consists of 21 items, and its validity and reliability with clinical and non-clinical samples in Turkey were demonstrated (12). It contains 7 items for each subscale, and each item is scored between 0 (never) and 3 (almost always). Items 3, 5, 10, 13, 16, 17, and 21 of the scale assess the level of depression; items 2, 4, 7, 9, 15, 19, and 20 measure the level of anxiety; and items 1, 6, 8, 11, 12, 14, and 18 assess the level of stress. According to the total score of the depression subscale, the following categorization is made: normal (0-4), mild depression (5-6), moderate depression (7-10), severe depression (11-13), and very severe depression (14 and above). According to the total score of the anxiety subscale, (0-3) is graded as normal, (4-5) mild, (6-7) moderate, (8-9) severe, and (10 and above) very severe. The total score of the stress subscale was graded as normal (0-7), mild (8-9), moderate (10-12), severe (13-16), and very severe (17 and above).

Psychological impact was assessed using the impact of event scale-revised (IES-R). The IES-R is a self-report scale consisting of 22 items that measures the level of symptoms experienced in the last 7 days between 0 (none) and 4 (very much). It comprises three subscales: avoidance of traumatic events, over-arousal, and re-experiencing (13). In the validity and reliability study of the Turkish version of the scale, the cut-off value of the scale was found to be between 24-33, sensitivity to be between 74.0-92.2%, and specificity to be between 70.7-81.0% (14).

Statistical Analysis

While the data were included in the paired comparison analysis, to identify individuals with high levels of worry, the items of the COVID-19 worry and attitude questionnaire were grouped as follows: often; almost always (high); never; rarely; and sometimes (low). Self-rated health status was analyzed as good-very good (high) and moderate-bad-very bad (low). To identify individuals with high psychological burden, we detected individuals with moderate, severe, and very severe DASS-21 depression, anxiety, and stress levels. A score of 33 was included in the analysis as the cut-off score on the IES-R scale. IBM SPSS for Windows 23.0 statistics software package (Armonk, New York: IBM Corp.) was used for data analysis. Categorical data are presented as

numbers (n) and percentages (%). Binary logistic regression analysis was used to detect factors that predicted high DASS-21 scores for depression, anxiety, stress, and IES-R. Test validity was determined using the omnibus test and the Hosmer-Lemeshow test. Explanatoriness of the regression analysis was determined using Nagelkerke R2. Logistic regression test results were presented using odds ratio and 95% confidence interval values. The cases where $p \leq 0.05$ were accepted as statistically significant.

RESULTS

A total of 633 participants completed the survey. Of the participants, 18.2% (n=115) were students, 42.2% (n=267) were actively employed, 22.7% (n=144) had flexible working arrangements (furloughed-rotation, working from home), and 16.9% (n=107) were unemployed. Of the entire group, 29.7% (n=188) had moderate, severe, or very severe depression, 19.3% (n=122) had moderate, severe, or very severe anxiety, %13.4 (n=85) had moderate, severe, or very severe stress. The IES-R score was detected above 33 points in 23.2% (n=147) of the patients. The severity of DASS-21 and IES-R scores and COVID-19 worry and attitude questionnaire scores are summarized in Table 1.

In the regression analysis, the variables that predicted moderate, severe, and very severe DASS-21 depression were active and flexible working, low self-rated health status, worry about social restrictions, financial difficulties, social breakdown, and getting COVID-19 test. (Nagelkerke R square =0.356, Hosmer-Lemeshow =0.476). The variables that predicted moderate, severe, and very severe DASS-21 anxiety were low self-rated health status, worry about spreading the virus to others, death of relatives from COVID-19, social restrictions, social breakdown, and access to adequate health care. Wearing a mask was significantly related to a decrease in individuals' anxiety levels (Nagelkerke R square =0.406, Hosmer-Lemeshow =0.720). In the regression analysis, the variables that predicted moderate, severe, and very severe DASS-21 stress were active working, contact history, worry about social restrictions, social breakdown, access to adequate health care, and taking the COVID-19 test (Nagelkerke R square =0.389, Hosmer-Lemeshow =0.725). The variables predicting high IES-R scores were flexible working, low self-rated health status, worry about spreading the virus to others, death of relatives from COVID-19, social restriction, social breakdown, and death from COVID-19 (Nagelkerke R square =0.394, Hosmer-Lemeshow =0.713) (Table 2).

DISCUSSION

In this descriptive study, it was observed that the most intense concerns of the participants during the pandemic were spreading the virus to others, getting infected, or the death of relatives. In addition, worries that commonly affected the participants' mental health included social restrictions and being alone. Additionally, 24.3% of the participants reported intense concerns about financial difficulties, 24.9% reported concerns about a social breakdown, and 14% stated their concerns about access to adequate health care. These results show that uncertainties regarding economic, social, and COVID-19 treatment cause worries in a significant percentage of the participants.

We found that worries about social restrictions have significant adverse effects on depression, anxiety, and stress levels in patients. Long-term social restrictions have been reported to lead to many negative consequences, such as a decrease in close interpersonal relationships, separation from friends and family, and a sense of loneliness (15-18). Previous studies have reported increased depression, stress, sleep disturbance, irritability, post-traumatic stress symptoms, and suicide risk among individuals during quarantine and isolation periods (19-22). Thus, while warning individuals to remain isolated during pandemics, it is important to educate and advise individuals on dealing with the negative mental effects of restrictions (23).

In this study, participants' concerns about financial difficulties were associated with an increase in the severity of depression. The COVID-19 pandemic has increased fears of economic crisis and recession, and widespread restrictions have caused economic uncertainty (24). In line with our study results, during the pandemic, it was reported that an increasing level of economic anxiety developed in individuals living in the community (25,26). We found that economic anxiety significantly predicted the severity of depression. Furthermore, we found that employment was associated with a decrease in depression, stress, and the psychological impact of the event. Consistent with our findings, having a regular income and working were found to be protective factors for mental health during the pandemic (3,17,27). On the other hand, the finding that worry about a social breakdown is a predictor on all scales in our study suggests that the socioeconomic uncertainty caused by the pandemic has led to widespread negative effects on individuals' mental health. In a previous study that investigated the most common worries of individuals related to the pandemic, participants reported many common major worries about social breakdown. The researchers emphasized that in the socioeconomic uncertainty, most individuals were concerned about the devastating impact of the virus on the health system, economy, and society (7). In addition to uncertainty, repetitive media exposure to community crises during the pandemic can lead to a higher perception of the current risk (7,28). The negative effects of these worries on

Table 1. Sociodemographic and clinical characteristics and pandemic-related worries of the participants			
		n	%
Gender	Female Male	394 239	62.2 37.8
Age	<30 30-50 >50	247 310 76	39 49 12
Education	Primary-high school University Masters-doctorate	73 397 163	11.5 62.7 25.8
Working status	Active employee Flexible employee Retired Unemployed Student	267 144 27 80 115	42.2 22.7 4.3 12.6 18.2
Monthly income	<5000 ₺ >5000 ₺	323 310	51.0 49.0
Marital status	Single Married	290 343	45.8 54.2
Having children	No Yes	308 325	48.7 51.3
Living situation	Alone Parents Spouse and/or children Friend(s)	63 204 344 22	10.0 32.2 54.3 3.5
Accompanying chronic disease	No Yes	495 138	78.2 21.8
COVID-19 contact history	No Yes	553 80	87.4 12.6
Self-rated health status	Low High	270 363	42.7 57.3
COVID-19 worry and attitude questionnaire			
Getting COVID-19 infection	Low High	485 148	76.6 23.4
Relatives getting COVID-19 infection	Low High	325 308	51.3 48.7
Spreading the virus to others	Low High	374 259	59.1 40.9
Death of relatives affected by COVID-19	Low High	466 167	73.6 26.4
Social restrictions	Low High	387 246	61.1 38.9
Access to food and provisions	Low High	610 23	96.4 3.6
Access to protective medical equipment	Low High	570 63	90.0 10.0
Financial difficulties	Low High	479 154	75.7 24.3
Social breakdown	Low High	475 158	75.0 25.0
Being kept in quarantine	Low High	585 48	92.4 7.6
Being alone	Low High	499 134	78.8 21.2

Table 1. Continued			
		n	%
Access to adequate healthcare	Low High	544 89	85.9 14.1
Getting COVID-19 test	Low High	582 51	91.9 8.1
Death from COVID-19	Low High	567 66	89.6 10.4
Wearing a mask	Low High	70 563	11.1 88.9
Handwashing/disinfection	Low High	80 553	12.6 87.4
Avoiding close contact	Low High	182 451	28.8 71.2
Scales			
DASS-21 depression	Normal Mild Moderate Severe Very severe	342 103 122 33 33	54.0 16.3 19.3 5.2 5.2
DASS-21 anxiety	Normal Mild Moderate Severe Very severe	425 86 61 27 34	67.1 13.6 9.6 4.3 5.4
DASS-21 stress	Normal Mild Moderate Severe Very severe	492 56 39 32 14	77.7 8.8 6.2 5.1 2.2
IES-R	0-33 >33	486 147	76.8 23.2

DASS-21: Depression, anxiety and stress scale; IES-R: The impact of event scale-revised, COVID-19: Coronavirus disease-2019

mental health demonstrate that social policies for the pandemic should be well-planned.

In this study, we determined that flexible working causes a decrease in IES-R scores. After the pandemic, a significant proportion of workers switched to remote work. It was reported that individuals who worked remotely during the pandemic were psychologically less affected by the event than active workers (27). Remote work and break periods can reduce the risk of exposure to COVID-19 and related concerns.

This study revealed that concerns about access to adequate healthcare were associated with participants' anxiety and stress levels. At the beginning of the pandemic, uncertainty regarding the treatment of COVID-19 was substantial. Hospitals and intensive care units were filled with patients with COVID-19. These developments may have led to an increase in treatment-related concerns. In connection with these worries, the present study found that worry about getting the COVID-19 test predicted depression and stress levels. Furthermore, some negative situations that may arise in cases in which the test is positive could trigger worry about getting tested: isolation, stigmatization, job loss, etc.

Another finding to emphasize is that the accompanying chronic disease was associated with the psychological impact of the event. These results imply that it is important to implement measures to protect vulnerable groups against the virus during the pandemic. Furthermore, self-rated health status was strongly correlated with levels of anxiety, depression, and the psychological impact of the event. These data are consistent with previous studies (2,5,29,30). Individuals who do not perceive their physical health well may worry about being infected or become more vulnerable to the virus. On the other hand, the stressful environment of the pandemic or the accompanying anxiety and depression can increase physical symptoms (31). Therefore, during the pandemic, individuals who do not find their physical health conditions appealing should be evaluated for accompanying mental disorders (2).

Table 2. Predictors of IES-R and moderate, severe, and very severe DASS-21 in binary logistic regression analysis

		Predictors	Sig.	EXP (B)	%95 CI Lower	%95 CI Upper
DASS-21 depression	**Sociodemographic**	Active employment	**0.006**	0.442	0.246	0.794
		Flexible employment	**0.007**	0.413	0.217	0.789
	Total	Active employment	**0.035**	0.480	0.242	0.951
		Flexible employment	**0.037**	0.454	0.215	0.955
		Self-rated health status (low)	**0.000**	2.257	1.459	3.491
		Social restrictions	**0.000**	2.632	1.676	4.134
		Financial difficulties	**0.008**	1.989	1.200	3.296
		Social breakdown	**0.010**	2.004	1.182	3.397
		Getting a COVID-19 test	**0.011**	2.615	1.242	5.505
DASS-21 anxiety	**Sociodemographic**	Gender (male)	**0.006**	0.516	0.322	0.827
	Total	Self-rated health status (low)	**0.000**	2.957	1.766	4.952
		Spreading the virus to others	**0.018**	2.151	1.139	4.063
		Death of relatives affected by COVID-19	**0.010**	2.194	1.204	3.997
		Social restrictions	**0.004**	2.195	1.281	3.759
		Social breakdown	**0.001**	2.738	1.494	5.016
		Access to adequate healthcare	**0.009**	2.350	1.241	4.453
		Wearing a mask	**0.023**	0.406	0.187	0.884
DASS-21 stress	**Sociodemographic**	Gender (male)	**0.005**	0.432	0.242	0.772
		Active employment	**0.011**	0.361	0.164	0.795
		Flexible employment	**0.026**	0.367	0.152	0.886
	Total	Active employment	**0.032**	0.359	0.141	0.913
		Contact history	**0.022**	2.964	1.172	7.494
		Social restrictions	**0.003**	2.585	1.379	4.844
		Social breakdown	**0.000**	3.423	1.755	6.676
		Getting a COVID-19 test	**0.029**	2.610	1.104	6.171
		Access to adequate healthcare	**0.044**	2.069	1.018	4.206
IES-R >33	**Sociodemographic**	Flexible employment	**0.003**	0.330	0.159	0.683
		Accompanying chronic disease	**0.004**	1.964	1.239	3.113
	Total	Flexible employment	**0.016**	0.340	0.142	0.815
		Self-rated health status (low)	**0.020**	1.753	1.093	2.810
		Spreading the virus to others	**0.002**	2.522	1.406	4.526
		Death of relatives affected by COVID-19	**0.003**	2.330	1.328	4.090
		Social restrictions	**0.002**	2.208	1.353	3.604
		Social breakdown	**0.007**	2.122	1.226	3.674
		Death from COVID-19	**0.024**	2.277	1.113	4.657

DASS-21: Depression, anxiety, and stress scale, IES-R: The impact of event scale-revised, CI: Confidence interval, COVID-19: Coronavirus disease-2019, EXP (B): Exponentiation of the B coefficient, Sig.: Significance

Consistent with our findings, worries about spreading the virus to others and the health of relatives were the most frequently reported concerns during the pandemic (2,7,26,32). We found that these worries significantly predicted high anxiety levels. Concerns about the health of relatives are consistent with data showing that coronavirus can be particularly dangerous in certain risk groups (advanced age, chronic disease, etc.) (7). In line with our findings, protective behaviors such as using masks could reduce anxiety (2). These concerns can also be mitigated by providing clear information to the public about threat risk, increasing the clarity of what they should do, and taking additional steps to protect vulnerable groups from the risk of infection (7,18).

In a climate of uncertainty, it is expected that people will be worried about their health, relatives, the economy, and the effects of the pandemic on society. However, intense and dysfunctional concerns associated with COVID-19 negatively affect individuals' mental health and should be considered therapeutic targets. In a study, Wahlund et al. (33) reported that online cognitive behavioral interventions targeting intensive and dysfunctional COVID-19-related concerns (e.g., illness, death, economy, family) are effective in reducing anxiety and improving mood, daily functioning, and intolerance to uncertainty. The findings of our study demonstrate the concerns about the pandemic that can be potential therapeutic targets and their significant adverse effects on mental health.

Study Limitations

This study has some limitations. The collection of study data using an online tool may have made it difficult to access risky elderly individuals and those with low socioeconomic status, in particular. The lack of assessment of media exposure among individuals can be considered a limitation because worries about the pandemic may be affected by media exposures. However, the fact that individuals' concerns about the adverse effects of the pandemic on the health system and socioeconomic conditions were investigated, and the scales validated in a normal clinical sample were used, could be mentioned as advantages.

CONCLUSION

During the pandemic, it is essential to take measures to protect individuals' mental health. Individual worries about their health, relatives, economy, and the effects of the pandemic on society have significant adverse effects on mental health. Social and health policies should be planned to reduce individual concerns during the pandemic.

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Ethics

Ethics Committee Approval: The Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee approved the study (approval number: 24237859-379, date: 19.06.2020).

Informed Consent: Individuals who read the informed consent form about the study via social media were asked to fill out the questionnaire.

Authorship Contributions

Surgical and Medical Practices: A.K., E.A., Concept: A.K., E.A., F.C.A., N.E.B., Design: A.K., E.A., F.C.A., D.S.A., N.E.B., E.Ö.K., Data Collection or Processing: A.K., E.A., F.C.A., Analysis or Interpretation: A.K., E.A., N.E.B., Literature Search: A.K., E.A., F.C.A., D.S.A., N.E.B., E.Ö.K., Writing: A.K., E.A., F.C.A., D.S.A., E.Ö.K.

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ORIGINAL ARTICLE

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Age-related Changes in Laboratory Test Results in Home Health Services: A Retrospective Study

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Abstract

Objective: Home healthcare services play a crucial role in reducing health expenditure, providing tailored care, and improving the quality of healthcare, particularly for managing chronic diseases.

Methods: This retrospective cross-sectional study analyzed the blood test and laboratory results of 1,461 patients who were evaluated by the home health services unit in Ankara between May 1, 2020, and July 31, 2020. The patients' ages, genders, and laboratory data were collected, and statistical analyses were performed using SPSS software. A p-value of <0.05 was considered statistically significant.

Results: The study included 1,461 patients, of whom 64.06% were female and 35.94% were male. Significant age differences were observed among the patients ($p<0.001$). Home visits were conducted for medical examinations and laboratory tests, and the results showed age-related variations in several parameters, such as albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase, creatine-kinase, gamma-glutamyl transferase (GGT), calcium (Ca), free triiodothyronine, free thyroxine, total protein, triglycerides, prothrombin time, activated partial thromboplastin time, urea, uric acid, creatinine, and potassium. Gender differences were also observed, with varying levels of amylase, activated partial thromboplastin time, ALT, total bilirubin, direct bilirubin, GGT, C-reactive protein, albumin, phosphorus, high-density lipoprotein cholesterol, Ca, and unsaturated iron binding capacity.

Conclusion: Considering age-related laboratory test results is crucial in home healthcare settings.

Keywords: Elderly healthcare services, home care services, sociodemographic factors, blood chemical analysis

INTRODUCTION

Advancements in science and technology, along with the widespread availability of healthcare services and the evolution of preventive healthcare practices alongside modern medicine, have contributed to an increase in average life expectancy. This trend is evident both globally and in Turkey, where life expectancy at birth has been steadily rising, paralleled by a growing elderly population (1). According to data from the Turkish Statistical Institute in 2020, life expectancy at birth in Turkey was 78.6 years during the period of 2017-2019. Additionally, the proportion of individuals aged 65 and older within Turkey's total population was 9.5% as of 2020. Notably, an estimated 1.5 million elderly individuals reside alone in Turkey, with one in every four households accommodating an elderly person (2).

Aging is an inherent physiological process accompanied by various mental and physical declines. With increasing age, there is a heightened susceptibility to chronic diseases and their associated complications, as well as issues such as joint ailments and cognitive decline. Consequently, there arises an urgent need for on-site evaluations of elderly individuals and the provision

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of medical care within their living environments, a need that will only intensify as the elderly demographic expands. Within the realm of home healthcare services, directly delivering care to individuals within their homes serves several paramount purposes, including reducing healthcare expenditures, ensuring personalized care, fostering familial support structures, expediting recovery, enhancing healthcare quality, and empowering patients and their families with better healthcare knowledge, thereby improving overall quality of life (3).

In Turkey, the inception of home healthcare services dates back to the implementation of the "regulation on the delivery of home care services" in 2005, which mandated the provision of such services by the private sector under the supervision of the Ministry of Health. Subsequently, in 2010, with the issuance of the "directive on implementation procedures and principles of home health services provided by the Ministry of Health", public institutions and organizations began to offer home healthcare services. By 2017, the responsibility for providing home healthcare services had been entirely transferred to hospitals (4).

Home healthcare services encompass a spectrum of medical interventions, including assessments, analyses, treatments, and rehabilitation services delivered within patients' homes as part of diagnosis and planned treatment protocols. These services also include prescribing medications, facilitating medical device usage, and generating reports on their application. Notably, the home healthcare framework mandates that patients be transferred to healthcare facilities when necessary. A significant proportion of home healthcare recipients are elderly individuals, many of whom have a history of chronic illnesses and medication use. It is imperative for the management of chronic conditions that individuals undergo blood tests conducive to medical evaluations within their home environment. The role of laboratory testing in clinical diagnostics has assumed heightened importance, with approximately 70% of disease diagnoses relying on laboratory results (5).

Advancements in science and technology, coupled with the accessibility of healthcare services and the evolution of preventive healthcare practices, have led to an increase in average life expectancy globally and notably in Turkey. With a growing elderly population, there is a significant need for on-site evaluations and medical care within their living environments. Home healthcare services play a vital role in addressing this need, offering personalized care, reducing healthcare costs, and improving the overall quality of life. However, there remains a gap in the provision of essential medical services, such as laboratory testing, in home settings. Therefore, the aim of this study was to assess the feasibility and effectiveness of conducting blood tests for elderly individuals receiving home healthcare services, with the hypothesis that integrating laboratory testing into home healthcare protocols can improve the management of chronic conditions and enhance the overall quality of care for elderly patients.

METHODS

Design and Patient Selection

This retrospective, cross-sectional, and observational investigation was designed. This encompasses an analysis of blood tests and laboratory findings for patients assessed by the home health services unit in Yıldırım Beyazıt University Yenimahalle Training and Research Hospital from May 1, 2020, to July 31, 2020. The study received approval from the Non-interventional Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (decision number: 2022/01, date: 13.01.2022).

Data on patient age, gender, and laboratory outcomes were extracted from the laboratory information system. In total, 36,923 test results from 1,461 patients were retrospectively analyzed. This analysis included averaging the laboratory findings for patients who underwent multiple evaluations and those obtained within the specified timeframe. Patients were categorized according to age and gender. A comprehensive evaluation of the laboratory results, including glycated hemoglobin (HbA1c)%, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), amylase, activated partial thromboplastin time (aPTT), aspartate aminotransferase (AST), vitamin B12, creatine kinase (CK), C-reactive protein (CRP), direct bilirubin, D-dimer, iron, ferritin, fibrinogen, folate, phosphorus, free triiodothyronine (FT3), free thyroxine (FT4), gamma-glutamyl transferase (GGT), glucose, high-density lipoprotein cholesterol (HDL-C), calcium (Ca), chlorine, creatinine, lactate dehydrogenase, magnesium, potassium, prothrombin time (PT), sodium, total bilirubin, total cholesterol, total protein, triglycerides, thyroid stimulating hormone (TSH), unsaturated iron binding capacity (UIBC), urea, uric acid and complete urine analysis was performed based on these groups. This was a retrospective study; thus, informed consent was not obtained.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 20.0, released in 2011; IBM Corp., Armonk, NY, USA). The distribution of interval data was assessed using either the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Data with a parametric distribution are

presented as mean ± standard deviation, and non-parametric distribution as median [interquartile range (IQR)]. The comparison between independent groups for parameters with a parametric distribution was conducted using Student's t-test, and the Mann-Whitney U test was used for parameters with a non-parametric distribution. When the comparison involved more than two groups, analysis of variance (ANOVA) and the Kruskal-Wallis test were used. The chi-square test was used for the analysis of ordinal data. A p-value of <0.05 was deemed statistically significant.

RESULTS

In this investigation, 936 (64.06%) of the examined patients were females, while 525 (35.94%) were males, all of whom were 18 years or older. 83.1% of the patients included in our study were 65 years or older. Across the entire patient cohort, the median age was 77 years (IQR =16), with females exhibiting a median age of 78 years (IQR =16) and males 75 years (IQR =17), indicating a statistically significant age gap (p<0.001). Patients were grouped according to their ages as 18-64, 65-74, 75-84 and over 85, and further investigations were performed according to these groups.

Home visits were arranged for all participants to undergo medical assessments and necessary laboratory examinations. Throughout the study period, biochemistry panels were ordered for 1,093 patients, and complete blood counts were conducted for 1,092 individuals. Hormone and biomarker tests were administered to 579 patients, coagulation profiles were obtained in 478, and glycosylated hemoglobin levels were monitored in 381 patients. Complete urinalysis was also performed in 63 patients.

Age group analysis revealed a statistical decline in albumin, ALP, ALT, AST, CK, GGT, Ca, FT3, FT4, total protein, triglycerides, PT, and aPTT values with increasing age (p<0.005, p=0.015, p<0.005, p=0.029, p=0.012, p<0.005, p<0.005, p<0.005, p=0.007, p=0.00, p=0.00, p=0.01, p=0.00). Conversely, significant increases were observed in urea, uric acid, creatinine, and potassium levels with age (p<0.005, p=0.001, p<0.005, p=0.01). Notably, significant differences were observed among various age groups for glucose, HbA1c, chlorine, and TSH levels, although these changes did not consistently trend upwards or downwards (Table 1). No significant variations were observed for the other evaluated tests.

Gender-based examination indicated that levels of amylase, aPTT, ALT, total bilirubin, direct bilirubin, GGT, CRP, and creatinine were notably higher in male patients (p=0.005, p=0.012, p<0.001, p=0.012, p<0.001, p<0.001, p<0.001, p<0.001). Conversely, albumin, HDL-C, Ca, and UIBC levels were significantly elevated in female patients (p=0.027, p<0.001, p<0.001, p=0.001) (Tables 2-4). No significant differences were observed between genders in the other tests.

Table 1. Non-parametrically distributed laboratory results according to age groups

	18-64 years			65-74 years			75-84 years			>85 years			
	n	Median	IQR	n	Median	IQR	n	Median	IQR	n	Median	IQR	p
Albumin	158	38.0	7.2	209	36.0	8.0	370	35.0	7.00	303	34.0	7.0	<0.005
ALP	103	95.0	54.0	130	90.0	48.5	232	84.0	42.50	191	82.0	47.0	0.015
ALT	165	16.0	13.3	224	13.0	10.7	389	11.0	8.00	319	10.5	6.0	<0.005
AST	185	20.0	9.5	223	19.0	8.0	389	19.0	8.00	318	18.0	7.0	0.029
CK	133	54.0	44.0	160	52.5	52.8	271	44.0	43.00	221	43.0	35.0	0.012
GGT	183	31.0	32.0	218	27.0	27.3	381	20.0	22.00	313	18.0	14.5	<0.005
Glucose	182	89.5	50.3	218	102.5	58.4	385	95.0	50.50	317	92.0	43.5	<0.005
HbA1c	55	6.3	2.3	83	7.3	2.3	150	6.8	1.83	93	6.3	1.4	<0.005
Ca	186	9.1	0.7	222	9.1	0.7	385	9.0	0.70	312	8.9	0.7	<0.005
Cl	157	103.0	5.8	187	102.0	6.0	327	103.0	5.00	256	104.0	5.0	<0.005
Crea	182	0.7	0.4	222	0.8	0.5	390	0.9	0.44	319	1.0	0.5	<0.005
Urea	184	33.3	17.1	223	40.8	25.5	388	45.0	20.78	318	52.2	35.3	<0.005
Uric acid	147	5.3	2.5	168	5.9	2.9	304	5.9	2.30	258	6.0	2.8	0.001
TSH	102	1.4	1.4	111	2.1	1.8	205	1.6	1.54	182	1.4	1.6	0.013
FT3	100	3.9	1.1	108	3.5	1.0	203	3.5	1.04	178	3.4	1.0	<0.005
FT4	98	14.8	4.7	110	14.0	3.9	203	14.0	3.30	178	13.6	3.5	0.007

IQR: Interquartile range, ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transferase, CK: Creatine kinase, GGT: Gamma-glutamyl transferase, HbA1c: Glycated hemoglobin, Ca: Calcium, Cl: Chlorine, Crea: Creatinin, TSH: Thyroid stimulating hormone, FT3: Free triiodothyronine, FT4: Free thyroxine

Table 2. Parametrically distributed laboratory results according to age groups

	18-64 year			65-74 year			75-84 year			>85 year			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	p
Potassium	165	4.06	0.57	220	4.22	0.56	385	4.22	0.55	316	4.23	0.57	0.01
PT	119	29.49	8.43	160	28.97	8.62	134	28.57	11.48	65	24.77	9.37	0.01
T. prot	126	65.71	6.77	158	64.71	6.62	284	64.28	5.92	235	63.12	6.32	0.00
Trig	135	147.08	129.43	170	149.19	123.24	305	127.79	85.32	255	117.38	58.75	0.00
aPTT	117	37.47	6.31	158	37.11	6.64	134	36.27	7.56	65	33.46	6.55	0.00

PT: Prothrombin time, T. prot: Total protein, Trig: Triglycerides, aPTT: Activated partial thromboplastin clotting time, SD: Standard deviation

Table 3. Parametrically distributed laboratory results according to gender

	Female			Male			
	n	Mean	SD	n	Mean	SD	p
Amylase	569	69.98	39.08	304	77.77	39.68	0.005
aPTT	301	35.85	6.83	173	37.51	6.96	0.012
T. bil	608	0.65	0.45	327	0.76	0.62	0.002
T. chol	563	191.3	52.8	302	166.8	44.6	<0.001

aPTT: Activated partial thromboplastin clotting time, T. bil: Total bilirubin, T. chol: Total cholesterol, SD: Standard deviation

Table 4. Non-parametrically distributed laboratory results according to gender

	Female			Male			
	n	Median	IQR	n	Median	IQR	p
Age	936	78	16	525	75	17	<0.001
Albumin	681	36	7	359	35	8	0.027
ALT	716	11	8	381	13	10	<0.001
CRP	659	5.7	13.45	349	9.8	25.45	<0.001
D. bil	597	0.11	0.07	324	0.13	0.09	<0.001
Potassium	471	3.4	0.7	252	3.3	0.79	0.001
GGT	705	20	21	370	24	25	<0.001
HDL	560	45	16	299	37	13.5	<0.001
Calcium	708	9.1	0.7	377	9	0.7	<0.001
Creatinin	717	0.79	0.46	376	0.96	0.52	<0.001
Magnesium	680	2	0.4	362	2	0.3	<0.001
UIBC	579	2.37	0.99	299	2.16	0.9	0.001

IQR: Interquartile range, ALT: Alanine transaminase, CRP: C-reactive protein, D. bil: Direct bilirubin, GGT: Gamma-glutamyl transferase, HDL: High-density lipoprotein, UIBC: Unsaturated iron binding capacity

DISCUSSION

The principal target population for home healthcare services is the elderly population (6,7). Accordingly, 83.1% of the patients included in our study were 65 years of age or older. In addition, we found the average age of female patients to be significantly higher than that of male patients, which is in line with the age-related findings of many similar studies conducted in the field of home healthcare services (6-8).

Albumin is the most abundant protein in the blood, accounting for approximately half of the total protein (9). In light of known age-related declines, it is expected that both the total protein content of the blood and the albumin level will decrease with age, unless diseases present cause increases in other proteins, such as globulins. Indeed, in many prior studies that have sought to evaluate the relationship between albumin and age, the albumin level has been found to decrease with age, although a number of other studies have observed the albumin

level to be within normal limits in healthy elderly people (10,11). In the present study, the albumin and total protein levels both decreased with age; however, the albumin level was significantly higher in female patients than in male patients. A number of studies have found the albumin level to be higher in male patients, although this difference was reversed during the postmenopausal period, with the albumin level being found to be higher in female patients. Due to their age, the majority of female patients included in our study could be expected to be in the postmenopausal period, which may explain their higher albumin levels than male patients.

It is important to note that changes in patients' albumin levels are reflected in their Ca levels (12). In this study, a significant difference was observed between the age groups in terms of Ca levels, which decreased with age. Moreover, female patients exhibited significantly higher Ca levels than male patients. If the serum albumin level of a patient is less than 4 g/dL due to the binding of Ca to albumin, the patient's total Ca level should be corrected using the following equation: corrected Ca = serum total Ca (mg/dL) + 0.8 × [4.0 - serum albumin (g/dL)] (13). In the present study, the albumin levels of 812 patients were found to be less than 4 g/dL. However, when we re-evaluated all of the Ca results following correction using the previously mentioned equation, we found that there was no statistically significant difference between the age groups (p=0.08). Given this change in results, physicians should calculate and use the corrected Ca level during follow-up given that the Ca level may initially be interpreted as low due to hypoalbuminemia among elderly patients receiving home healthcare. In other words, we believe that family physicians, who are likely to frequently encounter members of the elderly population, should be particularly careful in relation to the follow-up of patients' Ca levels because of the increasing frequency of hypoalbuminemia (10).

Previous studies have shown that both ALT and AST levels decrease with age (12). Although the exact mechanism underlying this decrease remains unknown, it is believed that a change in glucose-insulin metabolism may occur with age. The age-related decrease in fasting blood glucose levels observed in previous studies supports this hypothesis (14). In our study, although the patients' ALT and AST levels decreased with age, no significant difference was noted in terms of their glucose levels. The reason for this may be that the patients' blood samples were not always taken after eight hours of fasting. In addition, in the context of home healthcare services, the time between sample collection and cell separation via centrifugation is not standardized. This is relevant because it has previously been established that glucose levels in non-centrifuged samples decrease by 5-7% per hour due to glycolysis (15). Thus, we consider the HbA1c test to be more reliable than glucose or fasting glucose tests in relation to follow-up of patients with diabetic home care or those with suspected diabetes. However, although the ALT level was found to be significantly higher in male patients in our study, no gender difference was observed regarding the AST or glucose levels. Some previous studies have suggested that male patients are associated with higher AST and ALT levels (12,16).

A previous study found that the ALP level increases with age until menopause in female patients and then decreases during the postmenopausal period (17). In light of these findings, the ALP levels of the female patients included in this study may have been decreased because the majority of them were 65 years of age or older. We found no significant differences between the genders in our study.

Our study also evaluated the patients' CK levels, which has previously been observed to be directly proportional to age and body mass index (18). We found that CK levels decreased with age in both female and male patients.

In this study, the patients' triglyceride level was noted to decrease with age. A number of earlier studies have investigated the relationship between triglyceride levels and age and found that triglyceride levels increase with age (19,20). However, the patients included in our study were all home healthcare patients with nutritional status that differed from that of healthy individuals. It has been established that the lipid profile of a patient is directly related to that patient's nutritional status (21). Thus, we believe that the age-related decrease in triglyceride levels observed in the patients included in this study may be related to their nutritional status.

We did not identify any relationship between the patients' HbA1c levels and their age or gender. In the literature, a number of studies have sought to evaluate the relationship between HbA1c and age and have found that HbA1c levels either increase with age or are unrelated to age (22,23).

Although the patients' TSH levels were not found to be associated with age in our study, both their FT3 and FT4 levels were observed to have decreased. Some prior studies have reported that patients' TSH levels increase with age, whereas others have found that it is not related to age (24,25). In accordance with our findings, previous studies have shown that FT3 and FT4 levels decrease with age (26).

CONCLUSION

The majority of patients receiving home healthcare services are elderly. However, age-related reference ranges are not typically used for most clinical laboratory tests. As the data presented in our study and supported by findings previously reported in the literature show that some test results increase or decrease with age, physicians should consider age in relation to follow-up of relevant parameters. For example, in the case of an increase observed in a parameter that is expected to be low due to age, additional care should be taken, and the patient should be closely followed, even if the result is within the reference range.

Family physicians frequently work with members of the geriatric patient population. Moreover, in addition to physical examination, biochemical tests are recognized as an important aspect of patient evaluation. In this context, we suggest that it is important to be aware of the changes that occur in certain parameters with age among the elderly population and to keep them in mind during patient follow-up.

Ethics

Ethics Committee Approval: The study received approval from the Non-interventional Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (decision number: 2022/01, date: 13.01.2022)

Informed Consent: This was a retrospective study; thus, informed consent was not obtained.

Authorship Contributions

Surgical and Medical Practices: H.D.B., Concept: H.D.B., Design: H.D.B., F.E., Data Collection or Processing: H.D.B., F.E., H.B.Y., Analysis or Interpretation: H.D.B., F.E., H.B.Y., A.R.D., Literature Search: H.D.B., F.E., H.B.Y., A.R.D., Writing: H.D.B., F.E., H.B.Y., A.R.D.

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Serum Uric Acid and Calcium Levels As Predictors of Maternal and Fetal Complications in Preeclampsia: A Retrospective Study

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Abstract

Objective: To evaluate the association between serum uric acid and calcium levels and maternal and fetal complications in women diagnosed with preeclampsia. Early prediction, prevention, and management of preeclampsia are crucial for clinicians to improve health outcomes.

Methods: The study included 189 women diagnosed with preeclampsia who delivered between 34 and 40 weeks of gestation, alongside a control group of 205 women without hypertension who delivered within the same gestational period. Data were retrospectively collected from the hospital records.

Results: Pregnant women with preeclampsia had an average age of 30.9±6.3 years, which was significantly older than the 27.9±6.2 years in the control group ($p<0.05$). The average gestational week at birth was 37±1.7 in the case group and 38.0±1.4 in the control group, showing a significant difference ($p<0.05$). Emergency cesarean sections were more common in the preeclampsia group ($p<0.05$), whereas normal deliveries were prevalent in the control group ($p<0.05$). There were no significant differences in elective cesarean section rates between the groups. The case group had significantly higher rates of hospital stay, maternal intensive care requirement, intrauterine growth retardation, and in utero mort fetalis ($p<0.05$). Serum uric acid and calcium levels were significantly higher in the case group ($p<0.05$).

Conclusion: Serum uric acid levels were significantly elevated in women with preeclampsia and correlated with severe complications, including eclampsia and hemolysis-elevated liver enzymes-low platelet syndrome, as well as prolonged intensive care stays for newborns. However, serum calcium levels did not show a significant association with maternal and fetal complications, highlighting the need for further research to explore these relationships. Identifying significant predictors of preeclampsia, such as serum uric acid levels, can aid in the early detection and management of preeclampsia, potentially reducing the risk of severe complications. Further randomized, controlled trials are needed to confirm these findings and explore preventive strategies.

Keywords: Preeclampsia, serum uric acid, serum calcium, maternal complications, fetal outcomes

INTRODUCTION

Preeclampsia is a complex disorder that affects multiple systems and typically manifests in the latter half of pregnancy or following childbirth. It is defined by the onset of hypertension and proteinuria or the emergence of hypertension accompanied by significant end-organ dysfunction, with or without proteinuria. As a significant contributor to maternal and neonatal morbidity and mortality, understanding and managing this condition are crucial for improving pregnancy outcomes (1).

Globally, hypertensive disorders affect 5-10% of all pregnancies and are a leading cause of maternal mortality. Specifically, preeclampsia complicates approximately 4.6% of pregnancies worldwide, and its prevalence is influenced by factors such as the maternal age spectrum within populations and the proportion

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of first-time mothers (2-4). The condition not only poses risks due to the syndrome itself but also increases the likelihood of fetal mortality and morbidity through complications related to prematurity, which are triggered by the early induction of labor (1). The pathophysiology of preeclampsia involves several biochemical and vascular changes, including elevated serum uric acid levels, which result from diminished glomerular filtration rates and augmented tubular reabsorption. Additionally, the placenta's increased oxidative stress contributes to higher uric acid production. This cascade is further exacerbated by inadequate trophoblast invasion, leading to hypoxia and oxidative stress, which induces uric acid synthesis (5-7). Despite the established association between hyperuricemia and preeclampsia, research, including a meta-analysis of five studies, has demonstrated that uric acid levels measured before the 25th week of gestation do not predict the onset of preeclampsia. Furthermore, systematic reviews have indicated that serum uric acid levels are not predictive of preeclampsia complications (8,9).

In contrast, dietary interventions, such as calcium supplementation, have been explored for their potential to mitigate the risk of preeclampsia. Studies have shown varying outcomes concerning the timing of birth and birth weight in pregnant women who did or did not receive calcium supplements, suggesting a possible avenue for prevention (10).

Given the significant impact of preeclampsia on maternal and fetal health and the ongoing search for effective predictive markers and preventive measures, this study aimed to explore the roles of serum uric acid and calcium levels in influencing pregnancy outcomes among women diagnosed with preeclampsia. By examining these biochemical markers, we aim to contribute to a broader understanding of preeclampsia pathophysiology and management.

Therefore, this study was designed to assess the impact of serum uric acid and calcium levels on gestational outcomes in women with preeclampsia. Our aim was to elucidate whether these biochemical parameters could serve as reliable predictors of the development of preeclampsia and its associated complications. Given the mixed findings in the literature, our hypothesis was that elevated serum uric acid levels and altered calcium levels are significantly associated with adverse pregnancy outcomes in preeclamptic women.

METHODS

Study Design and Participant Selection

This investigation was conducted on 189 patients diagnosed with preeclampsia who delivered between 34 and 40 weeks of gestation from January 2017 to January 2020 at the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's obstetrics and gynecology department, forming the case group. The control group consisted of 205 healthy women without hypertension who gave birth within the same gestational age range. The inclusion criterion was gestational age between 34 and 40 weeks to exclude the impact of fetal outcomes associated with prematurity and postmaturity.

University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee approved the study (decision number: 283, date: 30.06.2020). This retrospective comparative study leveraged verbal consent from participants, with patient data collected via a review of medical records and an electronic patient information system. Key demographic and clinical data, including age, gravida, parity, delivery week, delivery method, complications, length of hospital stay, and intensive care requirement, were documented. Perinatal outcomes were assessed by birth weight, incidence of intrauterine growth restriction (IUGR), and neonatal intensive care unit (NICU) stay durations. Laboratory investigations included complete blood counts, renal function tests, liver enzyme tests, and serum levels of uric acid and calcium, considering the values at admission to preclude treatment effects.

Statistical Analysis

Descriptive statistics, including means, standard deviations, medians, ranges, frequencies, and ratios, were used to summarize the data. The Kolmogorov-Smirnov test was used to assess the distribution of variables. Quantitative data comparisons between independent groups were conducted using the independent sample t-test and Mann-Whitney U test. The chi-square test was applied to analyze qualitative independent data, with the Fisher test substituting when the chi-square test prerequisites were unmet. Receiver operating characteristic curve analysis determined cut-off values and effect levels, with both univariate and multivariate logistic regression analyses exploring effect levels. SPSS 27.0 software facilitated all statistical analyses. $P<0.05$ was accepted as statistically significant.

RESULTS

In this investigation, the case group's participants were notably older than those in the control group, with a statistical significance ($p<0.05$). The occurrence of comorbidities was also substantially higher in the case group than in the control group, presenting a significant difference ($p<0.05$). The gestational age at delivery was lower in the case group than in the control group, indicating a significant difference, as depicted in Figure 1. The frequency of normal vaginal deliveries was significantly

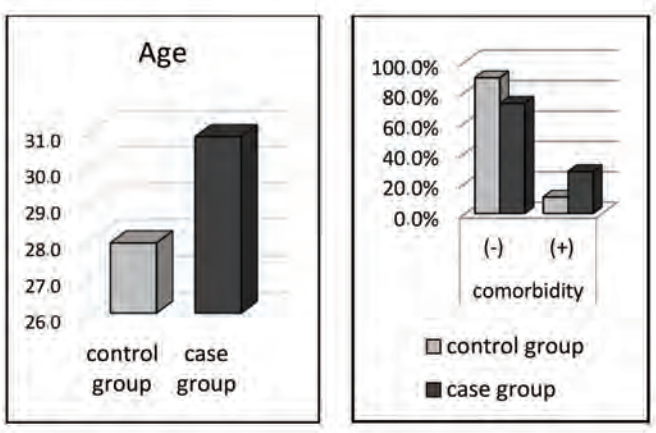

Figure 1. Comparison of age and comorbidity between control group and case group

reduced in the case group, whereas emergency cesarean sections occurred more frequently, both with statistical significance ($p<0.05$) as outlined in Table 1. However, the rates of elective cesarean section did not significantly differ between the two groups, as recorded in Table 1.

No significant disparity was observed in the gender distribution of newborns between both groups ($p>0.05$), as indicated in Table 1. Birth weights in the case group were notably less than those in the control group, and the difference was statistically significant ($p<0.05$), as detailed in Table 1. Appearance, pulse, grimace response, activity, respiration scores at both the 1st and 5th minutes post-delivery were significantly lower in the case group than in the control group ($p<0.05$), as shown in Table 1.

The incidence of maternal complications was significantly higher in the case group than in the control group ($p<0.05$),

Table 1. Comparison of case and control group

		Control group		Case group		p
		Ave.±SD/n %	Median	Ave.±SD/n %	Median	
Gestational age (weeks)		38.0±1.4	38.0	37.0±1.7	37.0	**0.000**[m]
Delivery	NVD	118 57.6%		38 20.1%		**0.000**[X²]
	CSE	68 33.2%		51 27.0%		0.181[X²]
	CSU	19 9.3%		100 52.9%		**0.000**[X²]
Gender	Male	106 51.7%		90 47.6%		0.417[X²]
	Female	99 48.3%		99 52.4%		
Fetal weight (gram)		3161.9±467.5	3180.0	2937.7±596.6	2990.0	**0.000**[t]
APGAR						
1 minute		7.4±0.8	7.0	6.9±1.7	7.0	**0.000**[m]
5 minutes		9.0±0.6	9.0	8.4±1.9	9.0	**0.001**[m]
Complications	(-)	198 96.6%		155 82.0%		**0.000**[X²]
	(+)	7 3.4%		34 18.0%		
HELLP		2 28.6%		13 38.2%		0.629[X²]
DIC		0 0.0%		7 20.6%		0.321[X²]
Eclampsia		0 0.0%		4 11.8%		1.000[X²]
Other		5 71.4%		10 29.4%		**0.036**[X²]
NICU (days)		2.0±3.9	0.0	5.8±9.0	0.0	**0.000**[m]
FGR	(+)	33 16.1%		48 25.4%		**0.022**[X²]
	(-)	172 83.9%		141 74.6%		
IUMF	(+)	0 0.0%		8 4.2%		**0.003**[X²]
	(-)	205 100.0%		181 95.8%		
Neonatal death	(+)	0 0.0%		1 0.5%		0.480[X²]
	(-)	205 100.0%		188 99.5%		
Maternal hospitalization duration (days)		1.7±0.7	2.0	2.9±1.5	3.0	**0.000**[m]

[t]Indipendent sample t-test, [m]Mann-Whitney U test, [X²]Chi-square test

NVD: Normal vaginal delivery, CSE: Cesarean section-elective, CSU: Cesarean section-urgent, HELLP: Hemolysis-elevated liver enzymes-low platelet syndrome, DIC: Dissemine intravascular coagulation, NICU: Neonatal intensive-care-unit, FGR: Fetal-growth-restriction, IUMF: In utero mort fetalis, APGAR: Appearance, pulse, grimace response, activity, respiration, Ave.: Average, SD: Standard deviation

as detailed in Table 1. Specifically, in the case group, HELLP syndrome was observed in 13 patients (6.8%), intravascular coagulopathy in 7 patients (3.7%), and eclampsia in 4 patients (2.1%). The duration of NICU stay was longer for the case group than for the control group, with a significant difference ($p<0.05$), as presented in Table 1. Additionally, the rates of IUGR, necessity for maternal intensive care, and length of maternal hospital stay were significantly higher in the case group than in the control group ($p<0.05$), as shown in Table 1. No significant difference was found in the neonatal mortality rates between the groups ($p>0.05$), reported in Table 1.

There was no significant distinction between the case and control groups in hemoglobin, platelet count, AST, LDH, and calcium levels ($p>0.05$), as indicated in Table 2. Conversely, pH, magnesium, and albumin levels were significantly lower in the case group, whereas ALT, urea, uric acid, creatinine, and corrected calcium levels were significantly higher ($p<0.05$), as depicted in Table 2.

The diagnostic utility of uric acid levels demonstrated significant efficacy in differentiating between the case and control groups, with an area under the curve (AUC) of 0.739 (0.690-0.788). A uric acid cut-off value of 4.34 mg/dL yielded a sensitivity of 66.1%, specificity of 69.3%, positive prediction of 66.5%, and negative prediction of 69.3%, as shown in Figure 2. Similarly, corrected calcium levels showed substantial discriminatory power, with an AUC of 0.706 (0.654-0.758). A corrected calcium cut-off value of 9.46 mg/dL provided sensitivity and specificity of 66.1% and 69.3%, respectively, with both positive and negative predictions of 66.5% and 69.3%, respectively, as depicted in Figure 2.

In groups stratified by uric acid levels (≤4.34 mg/dL and >4.34 mg/dL), the IUGR rate did not significantly differ ($p>0.05$), and

Table 2. Comparison of case and control group

	Control group		Case group		p
	Ave.±SD	Median	Ave.±SD	Median	
PH	7.3±0.1	7.3	7.0±1.5	7.3	**0.004[m]**
HB	11.7±1.4	11.9	11.6±1.5	11.6	0.560[m]
PLT (x10^3)	238.3±65.8	234.0	232.0±80.0	228.0	0.350[m]
AST	22.1±15.8	20.0	28.1±26.4	20.0	0.214[m]
ALT	12.7±18.7	10.0	19.8±28.2	12.0	**0.000[m]**
LDH	249.3±90.1	226.0	270.8±119.0	242.0	0.113[m]
Urea	17.1±5.1	17.0	19.9±6.9	19.0	**0.000[m]**
Uric acid	4.01±1.05	3.96	5.15±1.47	4.92	**0.000[m]**
Creatine	0.56±0.90	0.47	0.58±0.14	0.56	**0.000[m]**
Magnesium	1.97±0.20	1.95	1.90±0.22	1.86	**0.000[m]**
Albumin	3.46±0.27	3.46	3.23±0.37	3.21	**0.000[t]**
Calcium	9.24±0.33	9.23	9.46±0.40	9.52	**0.000[t]**

[t]Indipendent sample t-test, [m]Mann-Whitney U test

Ave.: Average, SD: Standard deviation, PH: Potential of hydrogen, HB: Hemoglobin, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Table 3. Comparison by uric acid levels

		Uric acid ≤4.34		Uric acid >4.34		p
		n	%	n	%	
FGR	(+)	40	19.4%	41	21.8%	0.557[X²]
	(-)	166	80.6%	147	78.2%	
Complications	(-)	195	94.7%	158	84.0%	**0.001[X²]**
	(+)	11	5.3%	30	16.0%	
Delivery	NVD	67	32.5%	52	27.7%	0.294[X²]
	CSE	103	50.0%	53	28.2%	**0.000[X²]**
	CSU	36	17.5%	83	44.1%	**0.000[X²]**

FGR: Fetal-growth-restriction, NVD: Normal vaginal delivery, CSE: Cesarean section-elective, CSU: Cesarean section-urgent

[X²]Chi-square test

the complication rates were significantly higher in those with uric acid levels >4.34 mg/dL (p<0.05), as outlined in Table 3. No significant correlation was found between uric acid levels and the rates of normal spontaneous delivery or elective cesarean section; however, the emergency cesarean section rate was significantly higher in individuals with uric acid levels >4.34 mg/dL (p<0.05), as shown in Table 3.

For groups categorized by corrected calcium levels (≤9.46 mg/dL and >9.46 mg/dL), no significant difference was observed in the rates of spontaneous delivery and elective cesarean section (p>0.05), as detailed in Table 4. Nonetheless, the rate of emergency cesarean section was significantly increased in those with a calcium level >9.46 mg/dL (p<0.05), as indicated in Table 4.

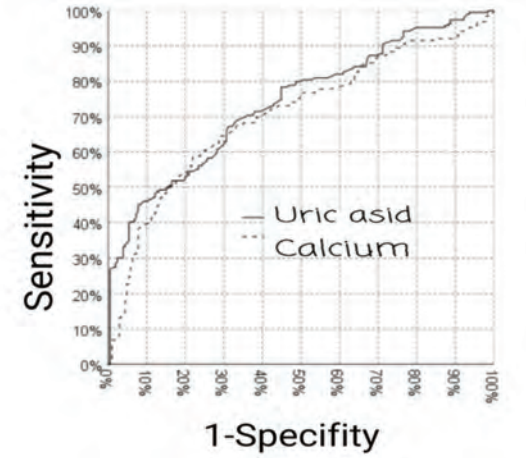

Figure 2. Receiver operating characteristic curves for uric asid and calcium

DISCUSSION

Preeclampsia remains a principal cause of maternal and neonatal morbidity and mortality worldwide. Despite extensive research, the exact etiology and pathogenesis of preeclampsia remain elusive, with prevailing theories suggesting endothelial damage and disrupted placental blood flow as key factors. Elevated serum uric acid levels resulting from compromised placental blood flow and oxygenation have been proposed as indicators of maternal and fetal distress. Given the life-threatening complications associated with preeclampsia for both mother and fetus, there is a continuous search for accessible and practical methods for its prediction and management. During the study period, our hospital recorded 8,927 deliveries, with 244 women diagnosed with preeclampsia, indicating a prevalence rate of 2.7%.

Earlier studies, such as those by Nair and Savitha (7), Shakarami et al. (11), Zhao et al. (12), and Vyakaranam et al. (13), demonstrated a correlation between elevated serum uric acid levels and preeclampsia, underscoring its potential role in disease progression and associated outcomes. Our findings resonate with these observations, revealing significantly higher serum uric acid levels in preeclamptic women than in their normotensive counterparts (p<0.05). Moreover, our analysis identified a significant increase in emergency cesarean sections among women with elevated uric acid levels (p<0.05), which is consistent with the association between high serum uric acid levels and the necessity for emergency deliveries demonstrated by Liu et al. (14).

The determination of the uric acid cut-off values in our study mirrors that of previous research (15,16), thereby indicating predictive sensitivity and specificity for preeclampsia. This finding reinforces the argument that serum uric acid is a valuable

Table 4. Comparison by calcium levels

		Calcium ≤9.46		Calcium >9.46		p
		n	%	n	%	
FGR	(+)	46	19.1%	35	22.9%	0.364$^{X^2}$
	(-)	195	80.9%	118	77.1%	
Complications	(-)	221	91.7%	132	86.3%	0.086$^{X^2}$
	(+)	20	8.3%	21	13.7%	
Delivery	VD	77	32.0%	42	27.5%	0.343$^{X^2}$
	CSE	104	43.2%	52	34.0%	0.070$^{X^2}$
	CSU	60	24.9%	59	38.6%	**0.004**$^{X^2}$

FGR: Fetal-growth-restriction, CSE: Cesarean section-elective, CSU: Cesarean section-urgent, VD: Vaginal delivery
X^2Chi-square test

marker for managing preeclampsia. However, contrasting findings from recent reviews and systematic analyses suggest a more nuanced relationship between serum uric acid levels and severe maternal and fetal outcomes, indicating the need for further investigation.

The role of serum calcium levels in preeclampsia has been debated, with studies by Sukonpan and Phupong (17), Kim et al. (18), and Jain et al. (19) suggesting lower serum calcium levels in preeclamptic women. Our study differed because it showed higher corrected calcium levels in preeclamptic patients, possibly attributed to adjustments for decreased serum protein levels in preeclampsia, which can affect calcium measurement. This discrepancy highlights the complexity of calcium's role in preeclampsia and underscores the importance of accurate calcium measurement in clinical assessment.

Study Limitations

This study's limitation lies in its focus on a population with generally low dietary calcium intake, potentially limiting the generalizability of findings related to calcium supplementation's impact on preeclampsia prevention. This finding underscores the necessity for larger-scale studies to comprehensively evaluate the effects of uric acid and calcium on preeclampsia in diverse populations.

CONCLUSION

Preeclampsia significantly affects maternal and neonatal health, emphasizing the importance of enhanced antenatal care, early detection, and effective management. The present study corroborates the association between increased maternal serum uric acid levels and a higher risk of complications in preeclampsia. Conversely, the association between serum calcium levels and preeclampsia remains ambiguous, suggesting the potential value of early pregnancy assessments of these markers. Elevated uric acid levels in patients with preeclamptic syndrome warrant caution, advocating for simple yet informative tests to mitigate the syndrome's complications. Further randomized controlled trials are necessary to confirm these findings and refine preeclampsia management strategies.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee approved the study (decision number: 283, date: 30.06.2020).

Informed Consent: This retrospective comparative study leveraged verbal consent from participants, with patient data collected via a review of medical records and an electronic patient information system.

Authorship Contributions

Surgical and Medical Practices: Y.A., Concept: Y.A., V.M., Design: Y.A., V.M., Data Collection or Processing: Y.A., Analysis or Interpretation: Y.A., Literature Search: Y.A., M.Ş., Writing: Y.A., M.Ş.

Conflict of Interest: Veli Mihmanlı is Associate Editor in European Archives of Medical Research. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review. Other authors have nothing to disclose.

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Rituximab Treatment Outcomes in Relapsed Primary Membranous Nephropathy: A Single-center Retrospective Study

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Abstract

Objective: Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults, with phospholipase A2 receptor (PLA2R) as its primary target antigen. This study assessed the treatment response to rituximab (RTX) in patients experiencing relapsed primary MN, focusing on its efficacy and impact on disease progression. This study aimed to evaluate treatment response to RTX in patients with relapsed primary MN, focusing on its effectiveness and correlation with anti-PLA2R antibody status.

Methods: Thirty-one patients meeting the inclusion criteria, including biopsy-confirmed MN diagnosis and relapsed disease, with an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2, were enrolled. Treatment response was assessed after six months, and patients were categorized into three groups: complete remission (CR), partial remission (PR), and unresponsive (UR).

Results: CR was observed in 6 patients (14.9%), PR in 13 patients (41.9%), and UR in 12 patients (38.7%). Serum anti-PLA2R antibody was positive in 19 patients (61.2%) pre-RTX, with 16 patients (84.2%) patients experienced seroconversion post-RTX (p=0.003). Significant increases in serum albumin and decreases in proteinuria were observed post-RTX (p<0.001). No significant difference in eGFR was noted (p=0.264).

Conclusion: These findings highlight RTX as a valuable treatment modality for relapsed primary MN, offering potential clinical benefits regardless of anti-PLA2R antibody status.

Keywords: Rituximab, membranous nephropathy, anti-PLA2R antibody, immunologic remission, glomerular filtration rate

INTRODUCTION

Membranous nephropathy (MN) is a prevalent cause of primary nephrotic syndrome in adults and is characterized by non-inflammatory autoimmune mechanisms involving subepithelial immune deposits localized within the glomerular basement membrane and podocyte (1). Primary MN accounts for the majority of cases (75 to 80 percent), driven by circulating autoantibodies against podocyte antigens, whereas secondary MN stems from various underlying conditions (2).

Among primary MN cases, the M-type phospholipase A2 receptor (PLA2R) emerges as a pivotal target antigen, with up to 80% of cases exhibiting anti-PLA2R antibodies, which are correlated with disease activity (3,4). Thrombospondin type-1 domain-containing 7A (THSD7A) is a transmembrane protein expressed on podocytes, and is the target antigen in approximately 3% of the primary MN cases (5). Additionally, several other target antigens such as, NELL1, SEMA3B, EXT1, and EXT2 have been identified, which are often associated with autoimmune disorders (1).

Clinically, MN typically manifests as nephrotic syndrome in 70-80% of patients, often presenting in the 4th to 5th decades of life and more prevalent in males. It is characterized by gradual onset proteinuria with hypertension and microscopic hematuria (6). Although renal biopsy has traditionally confirmed MN diagnosis, recent guidelines advocate for anti-PLA2R antibody testing in the absence of secondary causes (7).

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Initial management involves conservative measures and risk assessment for disease progression, with anti-PLA2R antibody levels as the guide for immunosuppressive therapy, considering the heightened risk of malignancy, especially in anti-PLA2R-negative cases (8). Rituximab (RTX), a monoclonal antibody targeting CD20-positive lymphocytes, has emerged as a promising therapeutic option, particularly in primary MN cases, owing to its B-cell depleting effects (9). Previous studies have demonstrated the efficacy of this regimen in inducing clinical and immunologic remission (IR) in primary MN (10,11).

Understanding the etiology and pathogenesis of MN is crucial for developing effective management strategies. Primary MN predominantly involves autoimmune mechanisms targeting podocyte antigens like PLA2R, whereas secondary MN arises from various underlying conditions. The identification of specific target antigens, particularly PLA2R, has revolutionized diagnostic and therapeutic approaches, emphasizing the importance of anti-PLA2R antibody testing in treatment decision-making. Despite advancements in the understanding of MN pathogenesis, optimal management strategies have remained unclear.

Current therapeutic approaches aim to alleviate symptoms, mitigate disease progression, and minimize treatment-related complications. Immunosuppressive therapy, guided by risk assessment and anti-PLA2R antibody levels, forms a cornerstone in the management of primary MN, highlighting the need for targeted therapies. RTX, with its B-cell depleting effects, presents a promising therapeutic option in primary MN management. Previous studies have demonstrated its efficacy in inducing remission, warranting further exploration of its treatment response, particularly in patients with relapsed disease.

By elucidating the efficacy of RTX in this context, we aim to contribute to the optimization of therapeutic strategies and improve outcomes in patients with primary MN. Therefore, this study was designed to evaluate the treatment response to RTX in patients with relapsed primary MN and assess its efficacy in achieving remission. The hypothesis of this study was that RTX treatment can significantly improve the clinical outcomes of patients with relapsed primary MN.

METHODS

Study Design

This retrospective study was conducted at a single center and was approved by the Erciyes University Clinical Research Ethics Committee (decision number: 2023/715, date: 25.10.2023), which adhered to the principles outlined in the Helsinki Declaration. Written informed consent was obtained from all patients.

The current study aimed to assess treatment response to RTX in patients with relapsed primary MN. Only patients aged 18 years or older were included in the study. The key inclusion criteria comprised a confirmed diagnosis of primary MN via pathological examination and disease relapse following first-line immunosuppressive therapy. Patients with an estimated glomerular filtration rate (eGFR) above 30 mL/min/1.73m^2 were eligible, whereas those with secondary MN, other renal diseases, diabetes mellitus, chronic liver disease, or immunosuppression therapy for another autoimmune condition were excluded.

The RTX treatment protocol consisted of an initial dose of 1 g followed by another 1 g dose after 14 days, in accordance with previous studies (10). Additionally, all patients received renin-angiotensin system (RAS) blockade agents. Treatment response was assessed after six months, and patients were categorized into three groups based on their response: complete remission (CR), partial remission (PR), and unresponsive (UR). CR was defined as a urinary protein-to-creatinine ratio (uPCR) <0.5 mg/mg accompanied by a normal serum albumin concentration, whereas PR was defined as a 50% reduction in proteinuria from the peak value, with uPCR between 0.5 and 3.5 mg/mg and an improvement in serum albumin concentration. UR referred to the failure to achieve either complete or partial response. Disease relapse was characterized by a return of proteinuria to ≥3.5 g/day after achieving CR or PR with immunosuppressive therapy, whereas IR entailed conversion from anti-PLA2R antibody positivity to negativity. Anti-PLA2R antibody detection was performed using enzyme-linked immunosorbent assay (ELISA) method. Antibody levels were measured twice, before RTX treatment and six months after treatment.

Statistical Analysis

To ensure data normality, histograms and q-q plots were examined, and the Shapiro-Wilk's test was applied. Descriptive statistics were employed to summarize numerical variables, which were presented as means and standard deviations or medians and quartiles depending on the data distribution. Categorical variables were summarized using frequencies and percentages. Group differences were assessed using either two-sided independent samples t-tests or Mann-Whitney U test for continuous variables, and Pearson's χ^2 analysis or Fisher's exact test for categorical variables. The Spearman correlation coefficient was used to explore the relationships between numerical variables. The Kruskal-Wallis test was applied to assess differences among the three groups for variables not following

a normal distribution. Statistical analyses were performed using TURCOSA statistical software (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr), with significance set at $p<0.05$.

RESULTS

A total of 31 patients (21 males, 10 females) with a mean age of 49.8±16.5 years were included in the analysis. The median disease duration before RTX therapy was 39 months (range: 21-121). Details regarding the demographic characteristics and laboratory findings of the patients before RTX administration are presented in Table 1.

Prior to RTX, all patients underwent various treatment regimens, with calcineurin inhibitors (CNI) (tacrolimus or cyclosporin A) and glucocorticoid combinations administered to all patients. Additionally, 19 patients (61.2%) received mycophenolate mofetil, while 5 patients (16.1%) received cyclophosphamide plus glucocorticoids. RAS blockade agents were also prescribed to all patients.

Table 1. Demographic features and laboratory results of patients.

Parameters	Results
Gender	
Male Female	21 (67.7%) 10 (32.3%)
Age (years)	49.8±16.5
BMI (kg/m^2)	26.82±4.36
Disease duration (months)	39 (21-121)
eGFR (mL/min/1.73m^2)	73 (50-112)
uPCR (mg/mg)	5.4 (2.9-7.8)
Albumin (g/dL)	2.8±0.3
Total protein (g/dL)	5.7±0.9
BUN (mg/dL)	20.6±6.6
Creatinine (mg/dL)	1.0 (0.8-1.3)
Sodium (mEq/L)	139.8±3.1
Potassium (mEq/L)	4.3±0.6
Calcium (mg/dL)	8.8 ±0.7
Phosphorus (mg/dL)	4.6±1.0
Uric acid (mg/dL)	6.3±1.7
Glucose (mg/dL)	97 (90-115)
LDL-Cholesterol (mg/dL)	143.8 (97-169)
Leukocytes (cell/µL)	9.380±3.068
Hemoglobin (g/dL)	13.51±1.52
Platelet (10^3/µL)	279.0±57.5

Values are expressed as mean ± standard deviation, median (1st-3rd quartiles)
BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, uPCR: Urinary protein to creatinine ratio, BMI: Body mass index, LDL: Low density lipoprotein

Following RTX treatment, the treatment response was as follows: CR in 6 patients (14.9%), PR in 13 patients (41.9%), and unresponsiveness in 12 patients (38.7%). Before RTX administration, serum anti-PLA2R antibody was positive in 19 patients (61.2%) and negative in 12 patients (38.8%). Post-RTX, 16 patients (84.2%) exhibited IR. Furthermore, among patients with IR, 14 (87.5%) achieved either CR or PR. A statistically significant correlation was observed between the antibody response of the patients and the treatment response ($p=0.003$). However, no significant correlation was found between initial proteinuria (or uPCR) and treatment response ($p=0.145$), nor between initial eGFR and treatment response ($p=0.179$), as illustrated in Figure 1. Moreover, age, body mass index, disease duration, serum albumin, electrolyte, and hemogram parameters were not correlated with treatment response. Similarly, no correlation was found between these variables and IR.

Sustained anti-PLA2R antibody positivity post-RTX was observed in only 3 patients (15.8%), all of whom exhibited UR. Conversely, among patients with negative anti-PLA2R antibodies at baseline, CR was observed in 2 patients (16.6%) and PR in 3 patients (25%). The distribution of IR according to treatment response groups is depicted in Figure 2.

Comparisons between the initial and sixth-month results revealed a statistically significant increase in serum albumin levels ($p<0.001$), as shown in Figure 3. Additionally, there was a significant decrease in uPCR values ($p<0.001$). However, no significant difference in eGFR values was observed ($p=0.264$), as summarized in Table 2.

DISCUSSION

In this study, we present the outcomes of RTX in patients with relapsed primary MN based on a single-center experience.

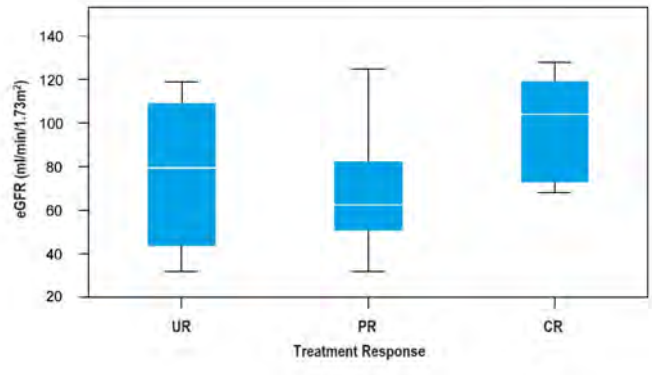

Figure 1. Initial eGFR of the patient's according to treatment response
eGFR: Estimated glomerular filtration rate, UR: Unresponsive, PR: Partial remission, CR: Complete remission

The data presented encompass the sixth month post-RTX treatment. Particularly noteworthy is the high treatment success rate observed in patients with anti-PLA2R antibody positivity. In patients with anti-PLA2R antibody positivity, complete or partial remission was achieved in 73.6% of patients receiving RTX. This outcome is not surprising for a disease with antibody-associated pathogenesis because RTX is known for its potent B cell depletion.

Our results emphasize the significance of anti-PLA2R therapy in disease prognosis and follow-up. No PR or CR proteinuria responses were observed in any patient in whom IR could not be achieved. Additionally, there was no proteinuria response (PR or CR) in only 2 patients (12.5%) in whom IR was attained. The kidney disease improving global outcomes (KDIGO) glomerular disease guidelines recommend anti-PLA2R antibody levels measured by ELISA and are valuable for informing initial treatment decisions when used in combination with clinical and laboratory parameters. Serum anti-PLA2R antibody level above 50 RU/mL is considered a high-risk predictor. Furthermore, high anti-PLA2R antibody levels and epitope spreading were associated with low RTX response in clinical studies (12).

We can approach MN treatment under the following two main headings; conservative approach and immunosuppression. KDIGO's recent glomerular disease guidelines recommend that in the treatment of MN, disease progression risk first be considered and then decide on an immunosuppression protocol. Treatment options include CNI, cytotoxic agents (such as cyclophosphamide), mycophenolate mofetil, RTX, and glucocorticoids.

RTX has taken its place in today's glomerulonephritis treatment guidelines (7). However, the optimal dosing regimen for RTX remains uncertain. The two most frequently preferred options are as follows. RTX 1 g was initially administered, followed 14 days later by another 1 g dose. An alternative regimen is to administer RTX 375 mg/m^2 weekly for 4 weeks. Furthermore, some experts offer B-cell monitoring for effective RTX dosage decisions (13). At our center, we administer RTX 1 g using a two-dose treatment protocol.

In the MENTOR study published in 2019, which examined 130 patients with nephrotic proteinuria, the RTX and CNI treatment arms were compared. At 12 months, 39 of 65 patients (60%) in the RTX group and 34 of 65 (52%) in the cyclosporine group had complete or partial remission. As a result, RTX was non-inferior to CNI in attaining complete or PR of proteinuria at 12 months (10). In another study recently conducted in Turkey in which two different dose groups were compared among 36 MN participants, a similarity was found between the two doses in terms of remission response (14). When compared with the literature data, the response rates to RTX treatment is similar.

In this investigation, we focused on RTX treatment outcomes in patients who received the first series of non-RTX immunosuppression therapy and subsequently developed disease relapse. We defined disease relapse as a return of proteinuria to ≥3.5 g/day after achievement of CR or PR with immunosuppressive therapy (7). In a study evaluating the prognosis of MN disease: the rate of remaining in remission was

Table 2. Alterations of laboratory parameters after RTX administration

Parameters	Initial	Sixth-month	Pearson χ^2
Serum albumin (g/dL)	3.3 (2.7-3.9)	3.9 (3.4-4.4)	p<0.001
uPCR (mg/mg)	5.4 (2.9-7.8)	1.7 (0.9-5.0)	p<0.001
eGFR (mL/min/1.73m^2)	73 (50-112)	75 (41-113)	p=0.264

RTX: Rituximab, uPCR: Urinary protein to creatinine ratio, eGFR: Estimated glomerular filtration rate

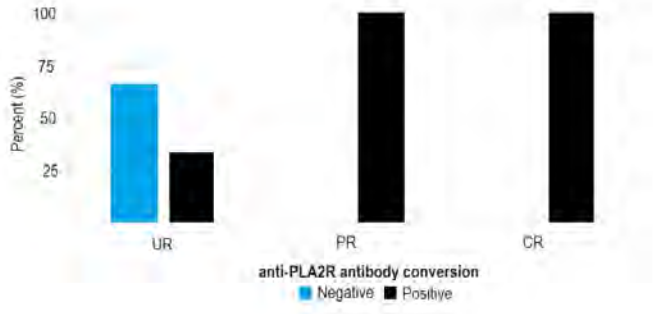

Figure 2. Anti-PLA2R antibody seroconversion according to the treatment response groups
UR: Unresponsive, PR: Partial remission, CR: Complete remission, PLA2R: Phospholipase A2 receptor

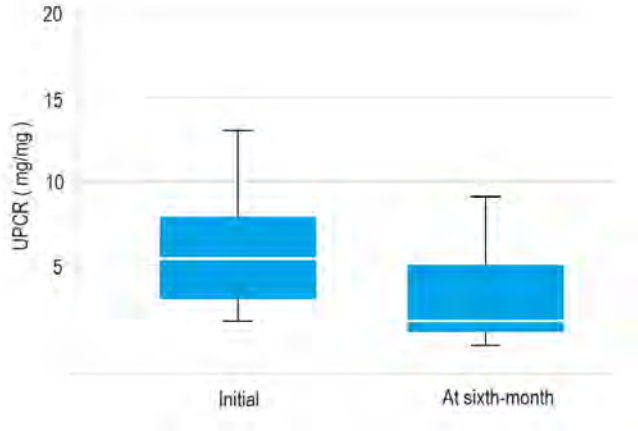

Figure 3. Changing in proteinuria level after rituximab administration
uPCR: Urinary protein to creatinine ratio

determined to be 67%, the rate of proteinuric relapse was 20%, and the rate of relapse accompanied by loss of kidney function was determined to be 13% (15).

The initial anti-PLA2R antibody seronegativity rate in our patient group was found to be 38.8%. This outcome is not far from the literature. The serum anti-PLA2R antibody positivity rate is reported in approximately 80% of primary MN patients (3). Antibodies developed against different antigens other than anti-PLA2R antibodies have been held responsible for the pathogenesis of the disease. The RTX treatment response rate was determined as 41.6% in patients with negative anti-PLA2R antibodies. When considered based on the mechanism of action of RTX, this rate can be thought high. However, there are a few suppositions that can be explanatory. First, there is the possibility of other responsible antibody positivity, such as anti-THSD7A antibodies, in these patients (16). Unfortunately, other antibodies responsible for pathogenesis are not commercially used in our country and are not assessed. Another possibility is that the antibody levels may have decreased to undetectable levels in the blood as a result of previous immunosuppression treatments, but the disease could be activated. The last option is that laboratory kits may not detect positivity.

Another important clinical consequence of immunosuppression is side effects. There were no RTX-related major side effects in these patients during the follow-up period. No major side effects, such as drug infusion-related anaphylaxis, life-threatening infections, or hepatitis B virus reactivation, were observed. Additionally, no life-threatening nephrotic syndrome complications were observed during the follow-up period of the patients, such as pulmonary embolism.

Study Limitations

The following are some limitations of our study: the treatment responses of the patients could be evaluated using histopathological data. The relationship between kidney biopsy findings and treatment response could be analyzed. However, this was a retrospective study. The kidney biopsy dates of some patients were too old, so we considered that these biopsies could not accurately reflect the actual nephron injury. However, Mirioğlu et al. (14) did not determine the relationship between RTX response and histological injury markers, such as sclerotic glomeruli, interstitial fibrosis, and tubular atrophy.

Furthermore, the follow-up period could be extended for long-term outcomes. In an RTX response analysis performed with 18 MN patients, 11.9 g/day baseline proteinuria decreased to 4.2 g/day and 2.0 g/day at 12 and 24 months, respectively (17).

CONCLUSION

Our data showed that RTX is an effective treatment agent for relapsed primary MN, and it can also be effective in patients with negative anti-PLA2R antibody. Due to this effect, it has already taken its place in first-line treatment in the current treatment guidelines. Optimal RTX dosing and treatment tips will be revealed with increasing clinical experience. We hope that the results we present will contribute to the global experience. Further randomized, controlled trials are needed to confirm these findings.

Ethics

Ethics Committee Approval: This retrospective study was conducted at a single center and was approved by the Erciyes University Clinical Research Ethics Committee (decision number: 2023/715, date: 25.10.2023), which adhered to the principles outlined in the Helsinki Declaration.

Informed Consent: Written informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: T.Y., İ.K., B.T., Concept: C.U., İ.K., M.H.S., B.T., Design: C.U., İ.K., Data Collection or Processing: T.Y., H.Ç., Analysis or Interpretation: C.U., H.Ç., M.H.S., B.T., Literature Search: T.Y., İ.K., Writing: C.U., H.Ç., M.H.S.

Conflict of Interest: No conflicts of interest were declared by the authors.

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ORIGINAL ARTICLE

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Prediction Scores of Mortality and Factors Affecting Morbidity in Trauma Patients in the Intensive Care Unit

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Abstract

Objective: Trauma is a significant public health issue with sociocultural and economic consequences that affect mortality and morbidity, resulting from both primary damage caused by direct impact and secondary damage. The aim of this study was to identify factors affecting mortality and morbidity in trauma patients admitted to the intensive care unit (ICU).

Methods: Demographic data on patients admitted to the ICU due to trauma between 2019 and 2021 were collected for the present study. Variables such as the acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA), and Glasgow Coma scale (GCS) scores, as well as the trauma score-injury severity score (TRISS), injury severity score (ISS), and revised trauma score (RTS), scores were recorded. Additionally, the use of vasopressors, development of renal failure, need for dialysis, and requirement for mechanical ventilation (MV) were documented for statistical analysis.

Results: The study included 194 trauma patients. The mean age ± standard deviation of the patients was 37.20±16.32 years. The most common cause of injury was traffic accidents (34.5%), with the head-neck region being the most frequently injured area (39.2%). The median length of stay in the ICU was 3 days (0-73), and the median number of days on MV was 0.25 days (0-73). Vasopressor medication was used in 34.5% of the patients, MV was required in 53.1%, septic shock was present in 4.1%, renal failure in 3.1%, hemodialysis was needed in 1.5%, and 51.5% required blood product replacement. Decreased GCS and TRISS scores and increased APACHE II, SOFA, and ISS scores were associated with increased mortality and prolonged ICU and MV days.

Conclusion: The results of our study showed that APACHE II and ISS scores were more sensitive than TRISS, SOFA, GCS, and RTS in predicting mortality in trauma patients, but the TRISS score was more reliable in predicting mortality.

Keywords: Trauma, intensive care, trauma scores, mortality, morbidity

INTRODUCTION

Trauma is a significant public health issue affecting mortality and morbidity. Trauma-induced functional impairment leads to disability and deteriorates health, delaying the achievement of functional independence (1). Many affected patients are severely or multiplely injured individuals, contributing to a higher rate of loss within the young population compared with other illnesses. Trauma cases require prompt diagnosis of anatomical and physiological damage, and prognosis should be determined during early intervention. It is critical to standardize these instances using objective criteria from both trauma scoring systems and scoring systems frequently utilized in intensive care units (ICUs) to accomplish this. The predictive scores for trauma mortality are inherently complex (2). Among these

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scoring systems, physiological scoring systems [Glasgow Coma scale (GCS), revised trauma score (RTS), pediatric trauma score (PTS), prehospital index, trauma triage rule, committee on risk assessment methodology] and anatomical scoring systems based on the type and severity of injury [abbreviated injury scale (AIS), injury severity score, trauma score-ISS (TRISS), new ISS, anatomic profile] stand out. Previous studies have reported that anatomical trauma scores better predict admission to ICU and physiological trauma scores better predict mortality (3).

It was suggested that the score should be very sensitive in predicting mortality risk and should be simple and rapid to apply in clinical settings. This approach makes it possible to gauge the severity of a condition, comprehend the variables influencing morbidity and mortality, take appropriate safety measures, avert unfavorable consequences, and enhance patients' quality of life all of which may lower healthcare expenses. The aim of the present study was to investigate the factors affecting mortality and morbidity using scoring systems developed for trauma patients and those used in intensive care.

METHODS

Study Approval and Ethical Considerations

This study complied with the Declaration of Helsinki's ethical criteria and was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital (decision number: 928, date: 05.06.2018). Prospective observation and descriptive analysis were conducted on the medical records of patients diagnosed with trauma treated at the department of anesthesiology and reanimation's ICU between November 2019 and November 2021. Informed consent forms were obtained from all patients.

Participant Selection and Data Collection

The inclusion criteria for this study were as follows: patients aged 18 years and above who have experienced non-vehicular traffic accidents, in-car traffic accidents, penetrating or cutting instrument injuries, falls from a height, firearm injuries, or assault. In addition, patients requiring intensive care due to trauma are included. Conversely, the exclusion criteria are as follows: patients under the age of 18, patients with vascular injuries who are being treated in the cardiovascular surgery ICU, and trauma patients with high American Society of Anesthesiologists (ASA) scores and advanced age who are being treated in the ICU for reasons unrelated to trauma.

Demographic data, type and severity of trauma, predominant injury site, hemodynamic parameters, and laboratory values at the time of initial ICU admission were recorded. The ISS, RTS, TRISS, acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA) score, and GCS were calculated.

The ISS calculation involved reducing the original nine body areas to a total of six: head (including neck), face, chest, abdomen, extremities (including pelvis), and soft tissue. The severity classification was then assigned to each of these bodily regions. The trauma score most commonly employed for research and statistical purposes is (4). The RTS is a numerical assessment derived from three variables: respiratory rate, systolic blood pressure, and GCS (5). The TRISS score is a comprehensive scoring method that incorporates anatomical and physiological data, including the RTS (physiological component), ISS (anatomical component), age, and injury mechanism, to assess and evaluate the data (6).

The following events were noted during ICU follow-up: the need for vasopressors; the presence of septic shock; renal failure; the need for dialysis; the quantity and type of blood replaced; the length of the ICU stay; the duration of mechanical ventilation (MV); the existence and severity of pressure ulcers; the existence of pneumonia associated with the ventilator; the ICU and 28-day mortality records; and the occurrence of re-admission to the ICU within 24 hours of discharge.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) (Chicago, IL, USA) version 24.0 software. The Mann-Whitney U test was used to compare continuous variables between two groups when parametric criteria were not met, and the chi-square test or Fisher's exact test was used to analyze categorical data. Utilizing receiver operating characteristic (ROC) analysis, the predictive powers of scoring systems in mortality prediction were assessed. In all analyses, a p-value of less than 0.005 was considered statistically significant.

RESULTS

A total of 235 patients were included in the study. Among the patients in the study, 12 were excluded because of their advanced age and high ASA score, whereas 10 patients were under the age of 18, and 19 suffered vascular injuries, and they were monitored in the cardiovascular surgery ICU. Consequently, 194 participants participated in the study. The demographic

data about the patients are presented in Table 1. The mortality rate of the patients was 19.6%. The TRISS-blunt (TRISS-B) score was mean ± standard deviation (SD) 79.57±32.43, the TRISS-penetrating (TRISS-P) score was mean ± SD 79.98±34.10, and the RTS score was mean ± SD of 6.27±2.05. The diagnostic values of the scoring systems for predicting mortality based on cut-off values are presented in Table 2, and the ROC curves are presented in Figure 1.

Table 1. Demographic data of the patients

Demographic data	**Mean ± SD, n (%)**
Age (years)	37.20±16.32
Gender, n (%)	
Female Male	15 (7.7%) 179 (92.3%)
Body mass index (kg/m²)	24.00±4.81
Chronic disease history, n (%)	
Yes No	32 (16.5%) 162 (83.5%)
Antithrombotic usage, n (%)	
Yes No	6 (3.1%) 188 (96.9%)
Mortality rate	38 (19.6%)

SD: Standard deviation

The median GCS, ASA, APACHE II, SOFA, and ISS scores of the patients were 13 [minimum (min)-maximum (max): 8-14], 1 (min-max: 1-1), 15 (min-max: 10-24), 3 (min-max: 1-6), and 18 (min-max: 13-29) respectively. The patients' RTS, TRISS-P, and TRISS-B scores were 6.27±2.05, 79.98±34.10, and 79.57±32.43, respectively, in terms of mean and SD.

In patients with an ISS score of 23 and above, the rates of MV requirement, development of renal failure, vasopressor requirement, and need for blood replacement were significantly higher ($p<0.001$, $p=0.040$, $p<0.001$, and $p<0.001$, respectively).

In patients with TRISS-B score below 84 and TRISS-P score below 73, the rates of MV requirement, vasopressor requirement, development of renal failure, and need for blood replacement were significantly higher ($p<0.001$).

In patients with a GCS score of 10 or below and an APACHE II score above 19, the rates of MV requirement, vasopressor requirement, development of renal failure, and need for blood replacement were significantly higher ($p<0.001$) (Table 3).

The median length of stay in the ICU was 3 (min-max: 0-73) days, with a mean ± SD of 9.28±14.2 days. The median duration of MV was 0.25 (min-max: 0-73) days, with a mean ± SD of 5.5±11.9 days. The distribution of MV days, ICU length of stay, and mortality rates according to scoring systems are presented in Table 4.

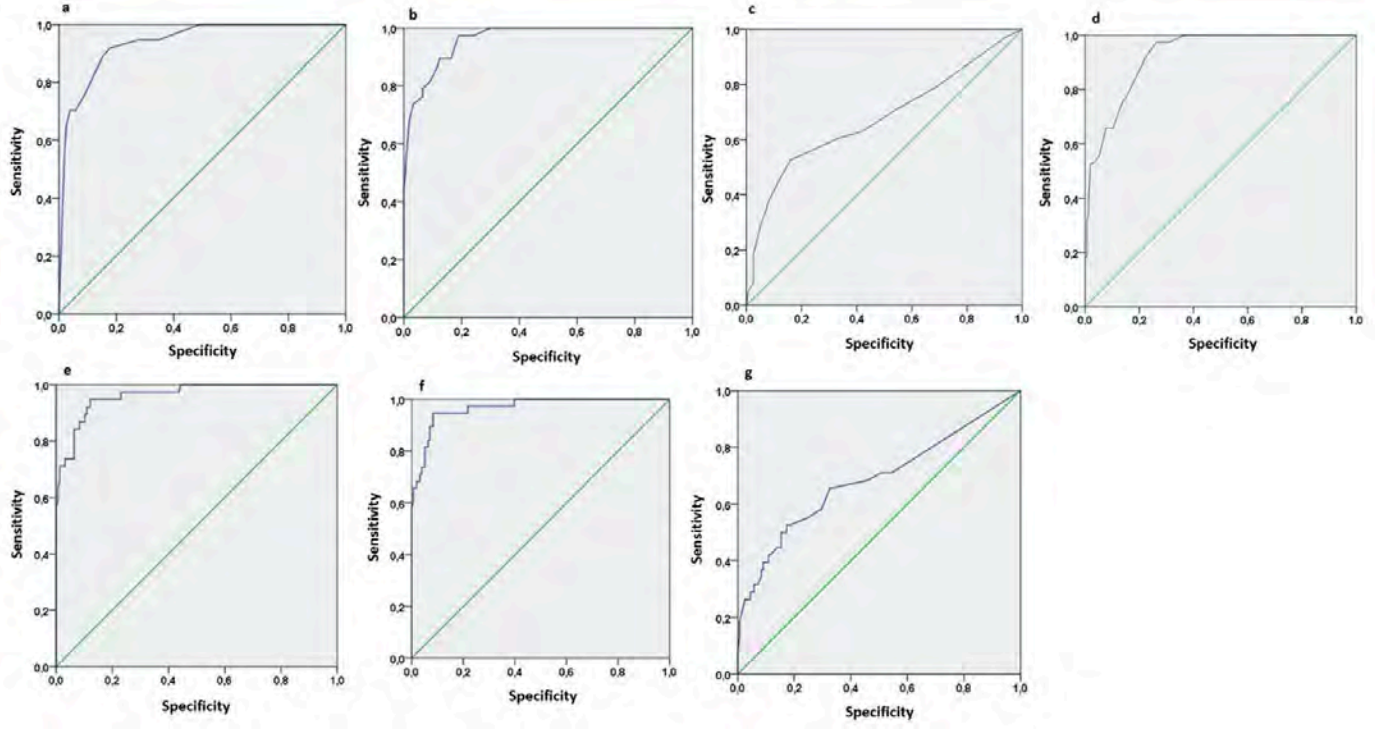

Figure 1. The ROC curves for mortality prediction of GCS (a), APACHE II (b), SOFA score (c), ISS (d), TRISS-B (e), TRISS-P (f), and RTS (g) are shown
ROC: Receiver operating characteristic, GCS: Glasgow Coma scale, APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment score, ISS: Injury severity score, TRISS-B: Trauma score-injury severity score-blunt, TRISS-P: Trauma score-injury severity score-penetrating, RTS: Revised trauma score

Table 2. Analysis of the diagnostic values of scoring systems in predicting mortality							
Cut-off value	**AUC**	**S.E.**	**OR (95% CI)**		**Sensitivity**	**Specificity**	***p**
GCS ≤10	0.93	0.02	0.89	0.97	0.91	0.82	<0.001
APACHE II >19	0.96	0.01	0.93	0.98	0.97	0.81	<0.001
SOFA ≥7	0.67	0.05	0.56	0.78	0.52	0.84	0.001
ISS ≥23	0.92	0.01	0.88	0.96	0.97	0.73	<0.001
TRISS-B <84	0.96	0.01	0.93	0.99	0.94	0.87	<0.001
TRISS-P <73	0.96	0.01	0.94	0.99	0.94	0.91	<0.001
RTS <5.63	0.68	0.05	0.57	0.79	0.52	0.82	<0.001

*Receiver operating characteristic analysis

OR: Odds ratio, CI: Confidence interval, AUC: Area under the curve, S.E.: Standard error, GCS: Glasgow Coma scale, APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment score, ISS: Injury severity score, TRISS-P: Trauma score-injury severity score-penetrating, TRISS-B: Trauma score-injury severity score-blunt, RTS: Revised trauma score

Table 3. Distribution of morbidity rates according to scoring systems				
	MV need	**Vasopressor need**	**Renal failure**	**Blood replacement**
GCS				
≤10	96.2%	60.3%	5.1%	75.6%
>10	24.1%	17.2%	1.7%	35.3%
APACHE II				
≤19	31.2%	13.6%	0.0%	37.6%
>19	92.8%	72.5%	8.7%	76.8%
ISS				
<23	28.4%	12.9%	0.9%	31.9%
≥23	89.7%	66.7%	6.4%	80.9%
TRISS-B				
<84	98.2%	74.5%	7.3%	89.1%
≥84	35.4%	18.7%	1.4%	36.7%
TRISS-P				
<73	98.0%	81.6%	8.2%	87.8%
≥73	37.9%	18.6%	1.4%	39.3%

*p-values are derived from chi-square test or Fisher's exact test. Data is presented as percentages

GCS: Glasgow Coma scale, APACHE II: Acute physiology and chronic health evaluation II, ISS: Injury severity score, TRISS-P: Trauma score-injury severity score-penetrating, TRISS-B: Trauma score-injury severity score-blunt, MV: Mechanical ventilation

The most common type of injury was traffic accident, accounting for a total of 34.5%, with non-vehicular traffic accident and in-car traffic accident being the most frequent subtypes. The head-neck region was the most commonly injured area, accounting for 39.1% of all injuries. Patients with head-neck injuries had the highest mortality rate at 31.6%. The highest mortality rate was observed in patients with in-car traffic accident at 34.5%. The distribution of mortality rates according to the type of injury and predominant injury regions is shown in Table 5.

34.5% of patients required vasopressor medication, 53.1% required MV, 4.1% developed septic shock, 3.1% developed renal failure, and 1.5% required hemodialysis. Blood product replacement was performed in 51.5% of the patients. Among the included patients, 9.8% required reoperation, 8.2% developed a need for ICU readmission after transfer to the ward, and pressure ulcers were observed in 17.5% of the patients.

Patients who required vasopressors had a significantly longer length of stay in the ICU and longer duration of MV compared with those who did not require vasopressors (p<0.001). The mortality rate among patients requiring vasopressors was 52.2%, which was significantly higher than that among those not using vasopressors (p<0.001).

Patients who developed septic shock, required blood replacement, required reoperation, or developed pressure ulcers had significantly longer lengths of stay in the ICU and longer durations of MV (p<0.005). Among the 8 patients who developed septic shock, mortality occurred in 5 (62.5%). The mortality rate of patients with septic shock was significantly higher than that of patients without septic shock (p=0.002) (Table 6).

The mortality rate was significantly higher in patients without a history of chronic illness than in those with such a history (p=0.021). Among patients who developed renal failure, those who required blood transfusion, and those who required dialysis, mortality was significantly higher compared with those who did not develop these conditions (p<0.001, p<0.001, and p=0.007, respectively).

DISCUSSION

Early diagnosis and intervention for trauma patients at high risk of death can lead to positive outcomes. Determining the extent of damage and gathering preliminary prognostic information are critical steps in triage for trauma patients. Various physiological

Table 4. Distribution of mechanical ventilation days, days of ICU stay, and mortality rates according to scoring systems			
	Mechanical ventilation days median (min-max)	**Days of ICU stay median (min-max)**	**Mortality rate median (min-max)**
GCS			
≤10	2.5 (0-73)	13.5 (1-73)	44.9%
>10	0 (0-43)	2 (0-48)	2.6%
APACHE II			
≤19	0 (0-43)	2 (0-50)	0.8%
>19	2.5 (0-73)	14 (1-73)	53.6%
ISS			
<23	0 (0-43)	2 (0-50)	0.9%
≥23	2 (0-73)	9 (1-73)	47.4%
TRISS-B			
<84	3 (0-73)	17.5 (1-73)	65.5%
≥84	0 (0-45)	2 (0-60)	1.4%
TRISS-P			
<73	3 (0-73)	17.5 (1-73)	73.5%
≥73	0 (0-45)	2 (0-60)	1.4%

*p-values are derived from Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables
Data is presented as median (minimum-maximum) for continuous variables and percentage for categorical variables
Min-max: Minimum-maximum, ICU: Intensive care unit, GCS: Glasgow Coma scale, APACHE II: Acute physiology and chronic health evaluation II, ISS: Injury severity score, TRISS-P: Trauma score-injury severity score-penetrating, TRISS-B: Trauma score-injury severity score-blunt

Table 5. Distribution of mortality rates by mechanism of injury and weighted injury regions		
Mechanism of injury	**n**	**Mortality (%)**
Stabbing/cutting injury	43	14.0
Falling from height	39	20.5
Non-traffic accident	38	15.8
Gunshot injury	36	19.4
Traffic accident	29	34.5
Assault	9	11.1
Injury region		
Head-neck	76	31.6
Vascular injury	26	7.7
Thorax	25	12.0
Abdomen	25	20.0
Extremity	17	5.9
Vertebral injury	10	0.0
Pelvic injury	10	20.0
Cardiac	5	20.0
Data is presented as number (n) and percentage (%)		

and anatomical scoring systems have been devised to provide clinicians with a suitable quantitative framework for decision-making (3).

Scoring systems should be simple, objective, and reliable and capable of accurately differentiating the severity of a patient's injury. The purpose of scoring systems is to ensure precise and prompt diagnosis and treatment of patients. A total of 194 patients were included in the study (mean ± SD age, 37.20±16.32 years). In a study conducted by Unlü et al. (7) on trauma patients, the mortality rate was determined to be 35.8%. Similarly, Kara et al. (8) found a mortality rate to be 19.4% in their study. In the present study, the mortality rate was 19.6%.

The GCS is commonly used as the gold standard to assess patient consciousness. A significant relationship between low GCS and mortality has been reported in previous studies (9-14). In the present study, the median GCS score was 13 (min-max: 8-14), and mortality was 44.9% in patients with a GCS ≤10. Additionally, in patients with GCS ≤10, the need for MV, duration of MV, duration of ICU stay, vasopressor requirement, need for blood replacement, and incidence of renal failure were statistically higher and longer than those with GCS >10.

The AIS and ISS are anatomical scoring systems, which indicates that they may be insufficient in distinguishing between patients with the same score but different hemodynamic status. Therefore, in 1987, Boyd et al. (6) proposed the TRISS system by combining the ISS and RTS while also taking into account the age factor. Studies have reported that the effectiveness of ISS in predicting mortality (%94.4 sensitivity, %60 specificity) is lower than that of TRISS and RTS, with TRISS demonstrating the highest effectiveness in predicting mortality and trauma outcomes. The

Table 6. Distribution of MV and ICU stay days by comorbidities				
Comorbidity	**MV days Median (min-max)**	**p**	**Days of ICU stay Median (min-max)**	**p**
Chronic illness				
Yes	0.8 (0-73)	0.142	3 (0-73)	0.395
No	0.5 (0-45)		3.5 (1-60)	
Antithrombotic use				
Yes	0.25 (0-73)	0.746	3 (0-73)	0.617
No	0.56 (0-20)		3 (1-20)	
Inotrope use				
Yes	0 (0-38)	<0.001	2 (0-50)	<0.001
No	2 (0-73)		9 (1-73)	
Septic shock				
Yes	0.25 (0-73)	<0.001	3 (0-73)	<0.001
No	43 (3-60)		45 (3-60)	
Kidney failure				
Yes	0.25 (0-73)	0.084	3 (0-73)	0.306
No	2.25 (0.25-9)		9 (3-9)	
Blood transfusion				
Yes	0 (0-18)	<0.001	2 (0-20)	<0.001
No	1.75 (0-73)		7 (1-73)	
Reoperation need				
Yes	0.25 (0-73)	0.034	3 (0-73)	0.032
No	2 (0-60)		6 (1-60)	
ICU re-admission				
Yes	0.18 (0-73)	0.004	3 (0-73)	0.012
No	3 (0-60)		7 (1-60)	

MV: Mechanical ventilation, ICU: Intensive care unit, min-max: Minimum-maximum
*P-values were calculated using the Mann-Whitney U test. Data is presented as median (minimum-maximum)

ROC value for TRISS was 0.963, whereas that for ISS was 0.854 (15,16).

Unlü et al. (7) reported a median TRISS value of 61, while Eryılmaz et al. (17) determined TRISS values for patients with fatal outcomes as 87.9±11.4. In our study, the mean ± SD TRISS-B was 79.57±32.43, and the mean ± SD TRISS-P was 79.98±34.10. TRISS-B [hazard ratio (HR): 0.967] and TRISS-P values were statistically associated with increased mortality (HR: 0.968). For TRISS-B, a cut-off value <84 had a sensitivity of 94% and specificity of 87% in predicting mortality. When the cut-off value for TRISS-P was determined as <73, the sensitivity for predicting mortality was 94% and specificity was 91%. The area under the ROC curve (AUC) results showed that compared with other trauma scores, TRISS-P provided the best prediction of mortality.

The median ISS value was 18 (min-max: 13-29), and a statistically significant relationship was found between an increase in ISS and an increase in mortality. When the cut-off value for ISS was determined as ≥23, the sensitivity for predicting mortality was 97%, with a specificity of 73%. Patients with TRISS-B cut-off value <84 and TRISS-P cut-off value <73 had statistically longer lengths of stay in the ICU and longer durations of MV.

An increase in the APACHE II score is significantly associated with mortality (7,8,18). Having an APACHE II score >19 has been found to be associated with mortality in trauma patients (19). In our study, the median APACHE II score was 15, and an APACHE II score >19 had a sensitivity of 97% and specificity of 81% for predicting mortality. Similarly, patients with an APACHE II score >19 had longer lengths of stay in the ICU and longer durations of MV.

A significant increase in the SOFA score (HR: 1.155) was found to be statistically associated with mortality. Although the mean SOFA admission score in the European trauma cohort was

reported as 5.1 (20), Brattström et al. (21) reported a median SOFA score of 5 in a study involving trauma patients. However, in our study, for a cut-off value of SOFA ≥7, the sensitivity for predicting mortality was 52%, with a specificity of 84%.

In a study involving 706 trauma patients, the SOFA score had discriminative power similar to APACHE II and TRISS in predicting outcomes of trauma patients in the ICU. The sensitivity of SOFA was found to be higher than that of APACHE II and TRISS, while its specificity was higher than that of TRISS but lower than that of APACHE II. The accuracy of SOFA was higher than that of TRISS but was not significantly different from that of APACHE II. In our study, however, the SOFA was found to have lower sensitivity compared with APACHE II (97%) and TRISS (94%), lower specificity compared with TRISS (TRISS-B: 87%, TRISS-P: 91%) but higher than APACHE II (81%).

It has been observed that the combination of anatomical and physiological scoring systems in the TRISS score provides better results in predicting the probable survival of trauma patients (22,23). The ability of TRISS to provide different survival predictions based on whether the trauma is blunt or penetrating also expands its utility in multiple traumas, thereby aiding clinicians. By encompassing physiological scoring like RTS and consequently GCS, as well as anatomical scoring like ISS, TRISS scoring becomes stronger compared to other scoring systems.

GCS, a physiological score incorporating systolic blood pressure and respiratory rate, has been reported to have a significant association with decreased RTS values and increased mortality rates, with mortality observed when the RTS cut-off value was <6.2 (7,17,18). In our study, however, the mean ± SD RTS was found to be 6.27±2.05, and no statistically significant relationship was observed between RTS and mortality. The sensitivity of predicting mortality for an RTS cut-off value <5.63 was 52%, with a specificity of 82% (AUC: 0.68). It was found that 42.6% of our patients with an RTS <5.63 had a fatal outcome. Given that most trauma patients are young and have potentially better compensatory mechanisms, initial RTS scores may be higher, making RTS alone insufficient for predicting mortality. Based on all these findings, we believe that in trauma patients, APACHE II and ISS scores are more sensitive for predicting mortality than TRISS, SOFA, GCS, and RTS.

In international studies conducted on trauma patients, it is stated that young people (15-45 years old) and males have a higher rate, and the majority of them do not have any comorbidities (7-9,18,24-27). In our study, 92.3% of patients were male, 7.7% were female, and 74.8% were aged 45 years or younger. The mortality rate was 16%, whereas 83.5% of the patients had no history of chronic illness, and the mortality rate among those without a history of chronic illness (34.4%) was higher. We believe that the high mortality rate among patients without a history of chronic illness in our study may be attributable to the exclusion of patients admitted to the ICU due to advanced age and high ASA scores. When the etiologies of the patients were examined, traffic accidents were found to be the most common. Trauma-related to traffic accidents was associated with mortality rates ranging from 49% to 52.4%, with head and neck injuries being predominant (8,10,21,28-30).

In our study, traffic accidents were found to be the most common cause of trauma, and a mortality rate of 50.3% was associated with these accidents. However, when examining the predominant injury sites of the patients, it was determined that head and neck injuries accounted for 39.2% of cases, with the highest mortality rate (31.6%) observed in this group. The lowest mortality rate (5.9%) was observed in patients with extremity injuries. Mortality was not observed in patients with vertebral injuries.

It is not surprising that trauma patients, particularly those with a high rate of erythrocytes (88%), require blood product transfusion (27). Kara et al. (8) reported that mortality was statistically higher in patients who received transfusions. In our study, 51.5% of patients received blood product replacement, and the mortality rate was higher among those requiring blood transfusion, with longer ICU and MV durations. Additionally, 3.1% of patients developed kidney failure, and 1.5% required hemodialysis; all of whom had fatal outcomes.

The high incidence of MV requirement in trauma patients has been significantly associated with mortality (8,18,27,31). In our study, MV was required in 53.1% of patients, and the mortality rate of 36.9% among these patients. In a study involving 9,721 trauma patients, the incidence of ventilator-associated pneumonia (VAP) was reported to be 5.6% (32), whereas another study with 4,111 trauma patients reported it to be 8% (33). In our study, VAP developed in 4.1% of our patients, and the differences in the incidence of VAP may be related to the number of patients and number of days under MV care. Brattström et al. (21) reported severe sepsis in 31.1% of trauma patients, whereas Dur et al. (31) reported sepsis in 20.3% of patients. In our study, 3.1% of patients developed septic shock, and 62.5% of those with septic shock had fatal outcomes. The mortality rate was higher in patients developing septic shock, and these patients had significantly longer ICU stays and MV durations. Patients requiring vasopressors tend to experience increased duration of ICU stay, prolonged MV duration, and increased mortality

(7,8,18,21,31). Dur et al. (31) reported that 14.5% of trauma patients required inotrope, and 77.7% of these patients had fatal outcomes. Brattström et al. (21) reported an average ICU stay of 3.1 days for trauma patients, Adıyaman et al. (18) reported a mean ± SD ICU stay of 14±16.2 days, Dur et al. (31) reported a mean ± SD ICU stay of 5±11 days, Kara et al. (8) reported a median of 3 days, and Unlü et al. (7) reported an ICU stay of 5 (1-139) days.

CONCLUSION

In conclusion, identifying factors contributing to mortality and morbidity in trauma patients admitted to the ICU is crucial for improving patient management. Factors such as GCS <10, TRISS-P <73, APACHE II >19, and ISS ≥23, the need for blood transfusion, vasopressor use, development of kidney failure, need for dialysis, prolonged invasive MV, and increased ICU stay duration are associated with increased mortality. The APACHE II and ISS scores are more sensitive in predicting mortality than the TRISS, SOFA, GCS, and RTS; however, the TRISS score is considered more reliable in predicting mortality.

Ethics

Ethics Committee Approval: This study complied with the Declaration of Helsinki's ethical criteria and was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital (decision number: 928, date: 05.06.2018).

Informed Consent: Informed consent forms were obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: C.K.B., Concept: C.K.B., Design: C.K.B., Data Collection or Processing: C.K.B., M.A., K.Y., Analysis or Interpretation: C.K.B., M.A., K.Y., T.M., N.T., Literature Search: C.K.B., M.A., K.Y., T.M., N.T., Writing: C.K.B., M.A., K.Y., T.M., N.T.

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ORIGINAL ARTICLE

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Investigation of 90Yttrium Radioembolisation Absorbed Radiation Dose to ALBI Scores in Liver Malignancies: Is It Safe Over 500 Gy Tumor Absorbed Dose with Voxel Based Dosimetric Approach? Preliminary Results

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Abstract

Objective: This retrospective study aimed to assess the correlation between absorbed doses using 90Yttrium (90Y) radioembolization and liver function test results in patients with primary or metastatic liver malignancies.

Methods: This study involved 35 patients diagnosed with primary or metastatic liver cancer who underwent treatment with 90Y glass microspheres. Absorbed doses of the tumor and perfused tissue were calculated using voxel-based dosimetry. Albumin-bilirubin (ALBI) scores were calculated before treatment and at 2 and 4 weeks post-treatment. Associations between the absorbed dose and ALBI scores were analyzed.

Results: Thirty-five cases were included in the study. The median radiation doses were 618 Gy for tumors, 497 Gy for the total perfused liver, 281 Gy for the perfused normal liver, 8.5 Gy for the normal liver, and 52.5 Gy for the total liver. Before treatment, 28 (80%) patients had grade 1 ALBI scores, whereas the remainder had grade 2 scores. In two patients, ALBI scores increased to grade 2 during the second week of treatment. Treatment response correlated with partial regression. Although their absorbed doses were not significantly higher than those of other cases (618/550 Gy for tumors, 116/97 Gy for perfused normal tissue, 12/8.5 Gy for normal liver), their tumor-to-whole liver ratios were significantly higher than those of other cases (27-35%). In one patient, the score increased to grade 2 in the fourth week of treatment. However, in this case, liver function failure was attributed to progressive disease post-treatment. None of the grade 2 patients' scores increased to grade 3.

Conclusion: The study concluded that, through voxel-based dosimetry and a selective treatment approach, higher tumor doses with low absorbed doses in the whole liver were safe.

Keywords: Radiation segmentectomy, 90Yttrium, dosimetry, radioembolization

INTRODUCTION

Around 75-80% of normal liver perfusion is facilitated by the portal vein. However, malignant lesions, particularly those larger than 2 cm, receive their blood supply from the hepatic artery. This dual blood supply characteristic makes locoregional therapies, such as radiofrequency ablation, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE), appealing options for managing liver malignancies.

90Yttrium (90Y) is a beta-emitting radionuclide (with an Eβ-max =2.28 MeV). 90Y-loaded microspheres have been employed

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worldwide for years for the radioembolization of primary and secondary liver cancers (1).

The objective of this study was to assess the impact of absorbed doses on liver function in patients undergoing high-absorbed doses during 90Y radioembolization.

METHODS

The study included 35 patients who underwent TARE using 90Y glass microspheres. Absorbed doses from hepatic artery perfusion scintigraphy images obtained using 99mTechnetium-labeled macroaggregate albumin were calculated using a voxel-based dosimetric approach using Simplicity^{Y90} (Mirada Medical, Oxford) software.

Albumin-bilirubin (ALBI) scores were calculated before, 2, and 4 weeks after treatment. Response to treatment was evaluated at 2 months after treatment according to the modified response evaluation criteria in solid tumours (RECIST 1.1) and positron emission tomography response criteria in solid tumours (PERCIST).

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2023.06.267, date: 22.06.2023). Informed consent form was obtained from all patients.

Statistical Analysis

Numerical variables are presented as median (range), whereas categorical variables are presented as percentages. Kruskal-Wallis tests were employed to compare ordinal variables among the groups. Additionally, the Mann-Whitney U test was used to assess the significance of pairwise comparisons.

Statistical significance was defined as a p-value of less than 0.05. All statistical analyses were executed using SPSS (version 22.0; IBM Corp, Armonk, New York, USA).

RESULTS

Thirty-five patients (17 females, 18 males) were included in the study. The median age was 64 years (range: 31-82) and the ages of male and female patients were similar. No serious treatment-related side effects were observed in any of the patients.

Twenty-two patients (63%) were diagnosed with hepatocellular carcinoma (HCC), 2 cases were diagnosed with cholongioselular carcinoma, and the others were metastatic cases (colon adenocancer: 7, neuroendocrine tumor: 3, breast ductal carcinoma: 1). Thirty-one (89%) patients were treated selectively and 4 (11%) were treated with the lobar approach.

The RECIST 1.1 and PERCIST treatment response evaluation results were similar. Treatment responses were as follows: 7 cases (21%) complete response (neuroendocrine tumor: 1, HCC: 6), 19 cases (53%) partial response (cholongioselular carcinoma: 1, breast ductal carcinoma: 1, neuroendocrine tumor: 2, colon adenocancer: 4, HCC: 11), 3 cases (8%) stable disease (colon adenocancer: 1, HCC: 2), 6 cases (18%) progressive disease (cholongioselular carcinoma: 1, colon adenocancer: 2, HCC: 3).

The median absorbed radiation doses were 618 Gy (range: 500-1000) for the tumor, 497 Gy (range: 270-843) for the total perfused liver, 281 Gy (range: 97-764) for perfused normal liver, 8.5 Gy (range: 1-49) for normal liver, and 52.5 Gy (range: 11-204) for the total liver. There were no significant differences between the absorbed doses according to gender and primary/secondary malignancy groups ($p>0.05$).

Before treatment, 28 out of 35 patients (80%) had grade 1 ALBI scores, whereas the remaining patients had grade 2 scores. In 2 HCC patients, ALBI scores improved to grade 2 in the second week of treatment. The treatment responses of these patients were consistent with partial response. Tumor, normal perfused and normal liver absorbed doses were 618/550 Gy, 116/97 Gy, and 12/8.5 Gy, respectively. The ratio of perfused normal liver volume to whole liver volume was only 0.2/0.7%. It was concluded that the absorbed doses were not significantly higher in these cases compared to all cases. However, tumor/whole liver volume ratios were significantly higher than those in other cases (27-35%).

In 1 metastatic patient, the score improved to grade 2 at week 4 of treatment. However, liver function failure was considered to be associated with progressive disease after treatment in this patient. None of the grade 2 patients experienced an increase in their scores to grade 3.

DISCUSSION

TACE has been a longstanding treatment for inoperable liver malignancies, and recent evidence indicates improved treatment responses and reduced side effects with TARE (2). TARE has emerged as a significant locoregional treatment option for both primary malignant liver neoplasms and liver metastases in cases unsuitable for surgery (3-5).

The ALBI score has superseded the Child-Pugh classification due to its ability to identify liver function decline at an earlier stage (6). Y90 is recommended for use in patients undergoing planned treatment and for monitoring post-treatment hepatotoxicity.

The advent of volumetric dosimetric methodology has signified a shift in our understanding of dosing strategies and subsequent treatment responses in radionuclide therapies. This approach by considering heterogeneity in the activity distribution within the perfused area, enables a more precise estimation of absorbed doses in both perfused tumor and normal tissue. Consequently, it facilitates the safe administration of higher tumor doses.

Initially, discussions regarding the tumor-absorbed dose ranged from 150-200 Gy in the early stages of treatment. However, recent publications have revealed the possibility of safe treatment escalation to up to 1000 Gy (7). Notably, a tumor response rate of only 22.5% was observed in cases of HCC with low tumor absorbed doses (8), a rate even lower than our recorded progression rate. Lam et al. (9) identified an independent correlation between predicted absorbed dose and survival. Our study's high tumor control rates further support the validity of this conclusion.

Kennedy et al. (10) reported transient mild-to-moderate liver-related toxicity in 94% of patients following TARE. They also highlighted that the delivered activity plays a role in toxicity. However, in their multicenter study, there was heterogeneity in activity calculation methods, and they lacked information on absorbed doses in tumor/non-tumor liver segments. In our study, no patient exhibited an increase in ALBI score grade due to high tumor-absorbed doses.

Given that a significant number of these patients had prior multiple chemotherapy treatments or cirrhosis, it is crucial to discern whether the ALBI grade escalation is attributed to TARE, concurrent diseases, or other therapeutic interventions. Typically, the anatomic response occurs later than the metabolic response (11). Surprisingly, in our case, both metabolic and treatment responses manifested similarly. This finding could potentially be linked to the administration of higher tumor-absorbed doses.

Study Limitations

Our primary limitation is the small cohort size. We intend to reevaluate our findings in a larger cohort to strengthen the robustness of our results.

Tailoring the optimal non-toxic dose for each patient through personalized treatment is a pivotal step in enhancing the success of TARE.

CONCLUSION

To conclude, employing voxel-based dosimetry and a tumor-selective approach to achieve high absorbed doses in the tumor while maintaining low doses in the normal liver is an effective and safe strategy for radioembolization treatment for suitable patient management.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2023.06.267, date: 22.06.2023).

Informed Consent: Informed consent form was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: E.A., Concept: E.A., B.E.A., Design: E.A., B.E.A., Data Collection or Processing: E.A., Analysis or Interpretation: E.A., B.E.A., Literature Search: E.A., Writing: E.A.

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ORIGINAL ARTICLE

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Hamatometacarpal Fracture-Dislocations: Clinical Evaluation, Treatment Strategies, and Outcomes

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Abstract

Objective: Hamatometacarpal fracture-dislocations (HMFD) are rare hand injuries resulting from axial loading. This study aimed to present the clinical presentation and outcomes of HMFD, which is rare and likely to be missed in the emergency department.

Methods: A retrospective analysis of 15 patients who underwent surgical intervention for HMFD between 2015 and 2023 was conducted. At the last follow-up, the presence of union, malunion, residual subluxation, and Kellgren-Lawrence grading scale were evaluated. Time to diagnosis, time to return to work (RTW), level of difficulty in working, grip strength, and disabilities of the arm, shoulder, and hand (DASH) scores were evaluated.

Results: The mean patient age was 30.6 years. Most injuries (93.3%) were due to punching. Open reduction was performed in 73.3% of cases. No complications were reported during the mean of 52.3-month follow-up. Open reduction was associated with a lower DASH scores. Hand-intensive work was correlated with a longer time to RTW and higher difficulty to RTW. Delayed diagnosis was correlated with worse grip strength, but not with significantly different DASH scores.

Conclusion: HMFD is a rare hand injury that presents as a diagnostic challenge. Achieving anatomical reduction is crucial for restoring hand function. Therefore, comprehensive treatment strategies should be planned individually, taking into account patients's injury patterns.

Keywords: Hamate, metacarpal bones, fracture-dislocation, grip strength, hand injuries

INTRODUCTION

Hamatometacarpal fracture-dislocation (HMFD) is a complex and challenging injury involving fracture and dislocation at the critical junction of the hamate and carpal bones of the hand. The anatomical region plays a crucial role in the function of the hand, and injuries in this area are particularly serious. Notably rare, HMFD typically result from traumatic events, such as falls, sports injuries, or direct strikes to the hand (1-4).

The combination of fracture and dislocation in this specific anatomical region can result in significant pain, swelling, and hand function loss. Ensuring an accurate diagnosis and appropriate treatment are essential to mitigate potential long-term complications and to facilitate an optimal recovery process. Diagnosing this rare injury is also challenging and can be easily missed in the emergency department when clinical and radiographic images are available (3,5). Undiagnosed HMFD may present with chronic joint dislocation, such as weak hand strength, chronic pain, and advanced osteoarthritis (6-8).

Although stable HMFDs can be treated with a circular cast after reduction is achieved with appropriate manipulation, unstable HMFDs require open reduction and internal fixation (1,3,5,6). Open reduction may be required in missed cases, and treatment with proximal metacarpal resection, carpometacarpal arthrodesis (CMC-A), or interposition arthroplasty may be required in cases in which open reduction is inadequate (2). The aim of this study was to present the clinical presentation and

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outcomes of HMFDs, which are rare and likely to be missed in the emergency department.

METHODS

Patients

Eighteen patients who were treated for HMFD between 2015 and 2023 were retrospectively reviewed. Patients who previously underwent hand surgery, had an inappropired radiograph, were under 18 years of age, and had a follow-up duration of less than 1 year were excluded. The current study included 15 patients (mean age 30.6±6.9 years) who underwent surgery for HMFD. Preoperative radiographs and computed tomography (CT) images were obtained from hospital picture archiving and communication system (Figure 1,2). The time to diagnosis was noted from the hospital database. The University of Health Sciences Turkey, Antalya Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (decision number: 3/9, date: 21.03.2024). This study was conducted in accordance with the tenets of the Declaration of Helsinki, and informed consent was obtained from all patients.

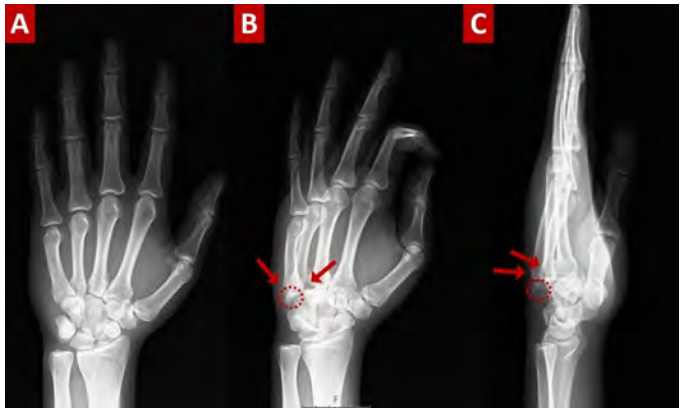

Figure 1. Preoperative anteroposterior (A), oblique (B), and lateral (C) radiographs of a 22-year-old male patient

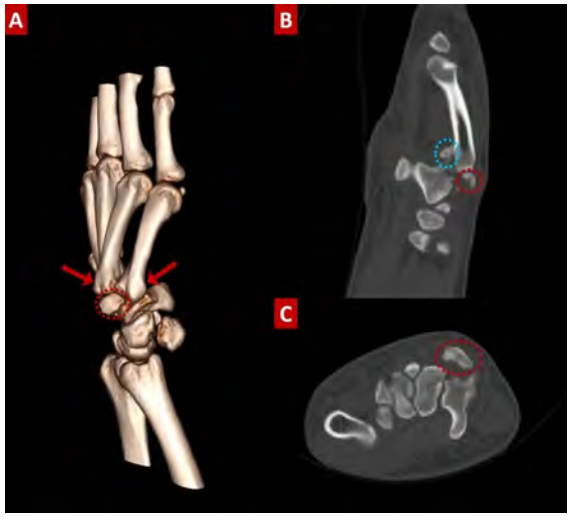

Figure 2. Preoperative three-dimensional (A), sagittal (B), and axial (C) CT scans of patient. Red arrows: 4 and 5 CMC dislocation, red circle: Dorsal fragment of the coronal hamate fracture, blued circle: Comminution of 4 metacarp basis
CT: Computed tomography, CMC: Carpometacarpal

Surgical Technique

The same surgical team performed all procedures under general or regional anesthesia. 2 g of cefazolin was administered for surgical prophylaxis before surgery. First, closed reduction was performed, and reduction was checked using fluoroscopy in cases that were considered as a stable injury preoperatively. If concentric reduction was obtained, it was fixed using Kirschner wires (K-wire). If unstable injury was considered preoperatively or concentric reduction was not obtained by closed reduction, open reduction was performed using the dorsal approach. The dorsal carpometacarpal (CMC) ligaments were repaired by suturing in all patients who underwent open reduction. Then, fixation was performed using K-wire, screw or plate depending on the size of the fragment (Figure 3,4). When the fragments were too small for fixation, dorsal soft tissue repair was performed, and a temporary K-wire was placed in the CMC joint (case 2,6,14). Additionally, CMC-A with plate was required in case 4 due to multiple comminutions of the fracture (Table 1).

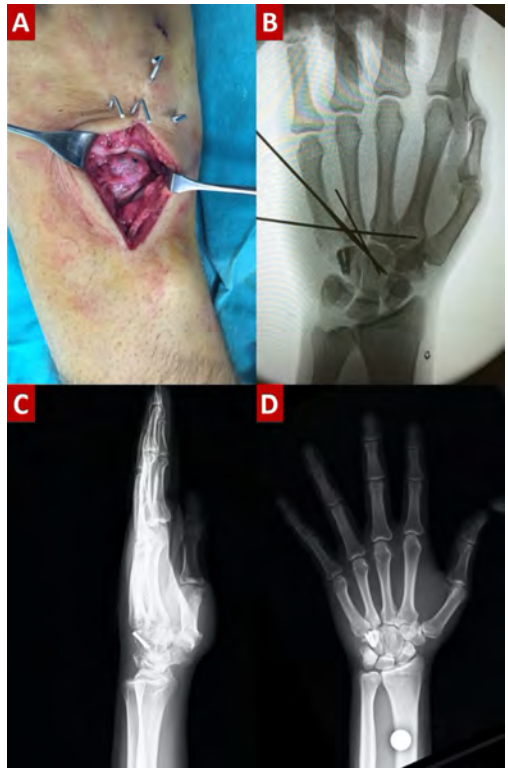

Figure 3. Intraoperative images of the dorsal approach (A) and anteroposterior fluoroscopy image (B). Postoperative lateral (C) and anteroposterior images (D).

Follow-up

The patients were immobilized in a cast for approximately 3 weeks. Metacarpophalangeal and interphalangeal range of motion (ROM) was allowed postoperatively. The K-wires were removed around 4 weeks. Strengthening exercises were initiated between 6 and 8 weeks.

Evaluation of Patients

All patients were evaluated clinically and radiologically. At the last follow-up, grip strength, and disabilities of the arm, shoulder, and hand (DASH) scores were assessed. Radiographs obtained during the final follow-up examination were utilized to evaluate the presence of union, malunion, residual subluxation, and Kellgren-Lawrence grading scale. Additionally, time to diagnosis, work, time to return to work (RTW), and difficulty in working were evaluated. If it was diagnosed before than 10 days it was noted as early diagnosis, otherwise it was noted as delayed diagnosis. The level of difficulty in working was assessed using patient responses categorized as "never", "mild", "hard", or "unable". Grip and fine hand skills required were defined as hand-intensive work (9).

Statistical Analysis

Descriptive data were expressed as mean ± standard deviation, median (minimum-maximum) for continuous variables, and number and frequency for categorical variables. As the group sample size was less than 50, the Shapiro-Wilk test was used to check for normality. The Mann-Whitney U test was used when the data did not follow a normal distribution, and the Student t-test was used to analyze differences between the measurements of the two groups. Categorical variables were evaluated using the chi-square test. Pearson's correlation coefficient (PCC) was used to analyze relationship between the continuous variables followed a normal distribution. P-values less than 0.05 were considered statistically significant.

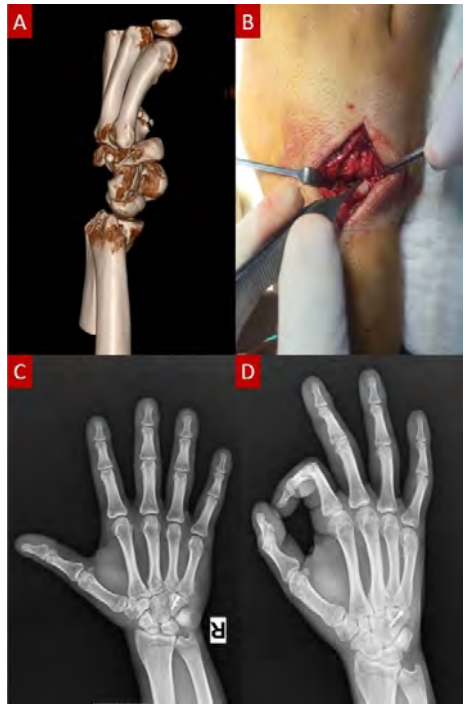

Figure 4. Preoperative three-dimensional scan (A) and intraoperative image of dorsal approach of patient (B). Postoperative anteroposterior (C) and oblique images (D) of patient

Table 1. Injury and treatment distributions of patients

Case	Hamate	Treatment	4th CMC	Treatment	5th CMC	Treatment	Reduction
1	F	Screw	FD	KW	D	KW	Open
2	F	None	FD	KW	D	KW	Closed
3	F	KW	None	None	FD	KW	Closed
4	F	CMC-A	None	None	D	CMC-A	Open
5	None	None	FD	KW	FD	KW	Closed
6	F	None	FD	KW	FD	KW	Closed
7	F	Screw	FD	KW	D	KW	Open
8	F	Screw	FD	KW	D	None	Open
9	F	Screw	FD	KW	D	KW	Open
10	F	Screw	D	KW	D	None	Open
11	F	KW	FD	KW	FD	KW	Open
12	None	None	FD	KW	D	KW	Open
13	None	None	FD	KW	FD	KW	Open
14	F	None	D	KW	D	KW	Open
15	None	None	FD	KW	FD	KW	Open

CMC: Carpometacarpal, F: Fracture, KW: Kirschner wire, CMC-A: CMC arthrodesis with plate, FD: Fracture-dislocation, D: Dislocation

RESULTS

All patients were male. The mean age was 30.6±6.9 (range, 18 to 45) years. Fourteen (93.3%) patients were right-handed, and 12 patients had a dominant-side fracture. The mean time to surgery was 17±30.6 (0-90). The injury mechanism consisted of 14 punching (93.3%) and 1 traffic accident (6.7%) (Table 2). Of the 15 cases, 11 (73.3%) underwent open reduction and 4 (26.7%) underwent closed reduction. The fracture configuration and fixation techniques were presented in Table 1. There were no complications. The mean follow-up was 52.3±32.5 (range, 12 to 102). The mean DASH score and grip strength were 21.1±8.9 and 81.7±19.5, respectively (Table 3).

Although the mean grip strength of the injured side was lower than that of the uninjured side, the difference was not statistically significant (p=0.580). While time to RTW was negatively correlated with grip strength (p=0.000, PCC =0.866), DASH score wasn't correlated (p=0.479; PCC=0.198). Although open or closed reduction did not affect grip strength and osteoarthritis (p=0.966, p=0.295; respectively), the DASH score was lower in the open reduction group (p=0.966). Time to RTW and difficulty in working were worse in the hand-intensive work group (p=0.003, p=0.019; respectively). Time to diagnosis did not affect time to RTW and difficulty in work (p=0.580 and p=0.057, respectively) (Table 4). Although grip strength and DASH score were worse in the delayed diagnosis group, only grip strength was significantly different (p=0.001 and p=0.173, respectively).

DISCUSSION

The results of this study revealed that HMFDs often necessitate open reduction for optimal alignment and stability. Although closed reduction with K-wire fixation may be sufficient for simple fractures, more complex and comminuted injuries require meticulous planning and consideration of various fixation techniques to achieve and maintain concentric reduction. Delayed diagnosis is associated with poorer outcomes, such as

Table 2. Descriptive data of the patients

		n=15
Age, mean ± SD (min-max)		30.6±6.9 (18-45)
Sex, n (%)	Male Female	15 (100) 0 (0)
Side, n (%)	Right Left	13 (86.7) 2 (13.3)
Dominant side, n (%)	Right Left	14 (93.3) 1 (6.7)
Injury mechanism n (%)	Punching	14 (93.3)
	Traffic accident	1 (6.7)
Open fracture, n (%)		0
Time to diagnosis (days)		17±30.6 (0-90)
Follow-up (months)		52.3±32.5 (12-102)

SD: Standard deviation, min: Minimum, max: Maximum, n: Number of patients

Table 3. Functional outcomes of patients

DASH, mean ± SD (min-max)	21.1±8.9 (10.8-45)		
Grip strength, mean ± SD	**Injured**	**Uninjured**	**p**
	81.7±19.5	96.2±8.6	0.580[1]
	Closed reduction	**Open reduction**	**p**
Grip strength, mean ± SD	81.4±11.9	81.9±22.1	0.966[1]
DASH score, mean ± SD	29.9±17.9	17.9±5.5	0.014[1]
	Early diagnosis	**Delayed diagnosis**	**p**
Grip strength, mean ± SD	93.3±5.3	64.3±20.3	0.001[1]
DASH score, mean ± SD	18.5±6.3	25.0±11.3	0.173[1]

DASH: Disabilities of the arm, shoulder, and hand, SD: Standard deviation, min: Minimum, max: Maximum, n: Number of patients
[1]Independent sample t-test

Table 4. Evaluation of patients according to osteoarthritis and return to work						
Kellgren-Lawrence						
		1	**2**	**3**	**4**	**p**
Time to diagnosis (n)	**Early**	6	2	1	0	0.363[1]
	Delayed	2	1	2	1	
Time to RTW Level of difficulty in work						
		Never	**Mild**	**Hard**	**Unable**	**p**
Time to diagnosis (n)	**Early**	6	3	0	0	0.057[1]
	Delayed	1	5	0	0	
Hand intensive work (n)	**No**	6	2	0	0	**0.019[1]**
	Yes	1	6	0	0	
Implant types (n)	**Temporary**	5	4	0	0	0.398[1]
	Permanent	2	4	0	0	
CMC dislocation configuration (n)	**4**	1	1	0	0	0.875[1]
	5	1	2	0	0	
	4-5	5	5	0	0	
Time to RTW (days)						
Time to diagnosis, mean ± SD	**Early**	**Delayed**				**p**
	6.1±1.5	6.8±3.4				0.580[2]
Hand intensive work, Mean ± SD	**No**	**Yes**				**p**
	4.9±1.1	8.1±2.2				**0.003[2]**
Implant types, mean ± SD	**Temporary**	**Permanent**				**p**
	6.9±2.8	5.6±1.4				0.343[2]
CMC dislocation configuration, mean ± SD	**4**	**5**	**4-5**			**p**
	6.0±2.8	6.7±3.1	6.4±2.4			0.959[2]

CMC: Carpometacarpal, RTW: Return to work n: Number of patients, SD: Standard deviation
[1]Pearson chi-square test, [2]Independent sample t-test

decreased grip strength and increased DASH scores. Furthermore, this study investigated the socioeconomic implications of HMFDs, revealing that individuals engaged in hand-intensive work face challenges when returning to work.

Fracture-dislocation of the metacarpophalangeal joint is a very rare injury. The main mechanism of injury is axial loading. The degree of palmar flexion of the fifth metacarpal significantly affects the type of hamate injury. Substantial flexion can cause dorsal dislocation of the base of the fifth metacarpal, damage to the dorsal CMC ligament, and dorsal fracture of the hamate. A longitudinal coronal fracture of the hamate occurs with slight flexion of the fifth metacarpal. Fracture-dislocation was observed in 14 cases following punching and in one case following a traffic accident. Because both 4 and 5 are flexed during punching, the most common combination was both 4 and 5 CMC dislocations (66.6%), with the remainder comprising isolated 4 dislocations (13.3%) and isolated 5 CMC dislocations (20%). In addition, all patients had dorsal dislocation. According to the literature, flexing the carpal bones is flexed during axial loading leads to dorsal dislocation, which is the most common dislocation (3,10). These results demonstrated that axial loading was the most prevalent mechanism of injury, consistent with the literature.

Diagnosing HMFDs is challenging because of the limited diagnostic capability of anteroposterior and lateral radiographs during the initial evaluation (11). Therefore, a missed diagnosis is very frequently seen (3,12). The fourth and fifth CMC joints have a greater ROM than the second and third (13). Misdiagnosis and delayed treatment can therefore lead to complications such as malunion, residual subluxation, arthritis and functional impairment. Misdiagnosis and delayed treatment can lead to complications such as malunion, residual subluxation, arthritis, and functional impairments (6). Therefore, additional oblique views and CT scans are essential in suspected cases (3,14). In the current study, diagnosis was possible in only six patients at initial presentation in the emergency department. Three cases were diagnosed after orthopedic evaluation was conducted

within 3 days. In all cases, CT scan was required for diagnosis. The remaining six cases were diagnosed clinical suspicion caused from persistent symptoms during subsequent early and late follow-up assessments. Although radiography is limited in its ability to evaluate patients with HMFD, CT is considered the gold standard. However, it should be noted that suspicion is the most crucial step in the diagnostic process. A delay in diagnosis is associated with poorer clinical outcomes (7,8). Delayed treatment causes prolonged immobility, difficulty in reduction, and increased requirement for open reduction (15). The current study demonstrated that delayed diagnosis may have a negative impact on grip strength and the DASH score. However, no relationship was found between time and diagnosis and difficulty with work or RTW.

Aim of the surgery is to achieve anatomic reduction of intra-articular fractures and concentric joint reduction. Inadequate treatment may cause malunion and residual subluxation (6). Although surgeons should prefer a suitable combination of reduction (open/closed) and fixation (K-wire, screw and plate) techniques, there is no consensus on an optimal treatment approach. The reduction can be achieved by both open and closed. However, it is difficult to maintain reduction with conservative treatment (14). Although open reduction and internal fixation techniques are commonly preferred in cases of delayed diagnosis, closed reduction and K-wire fixation is more commonly preferred in cases of early diagnosis, with isolated dislocations with or without comminuted small fragments. Closed reduction with K-wire fixation challenges to achieve concentric reduction by fluoroscopy. Therefore, it should be preferred for more stable fractures. Furthermore, it has been proposed that this approach may be preferable in cases diagnosed within the first 10 days (12). According to Lee et al.'s (16) treatment algorithm, hamate fractures with less than one-third articular surface involvement should be treated with closed reduction and K-wire fixation. Conversely, fractures exceeding one-third of the articular surface or those in the coronal plane should undergo open reduction and internal fixation by a dorsal approach (16). In the current study, open reduction was the most preferred approach (73.3%), and the latest closed reduction was performed at 14 days.

The treatment of an intra-articular fracture requires the achievement of anatomic reduction and rigid fixation. Screws are the optimal option for facilitating interfragmentary compression and rigid fixation. Headless screws and headed screws with or without a washer may be used (11). Unfortunately, there has been no compression study on the use of these screws in HMFDs. Nevertheless, screws are more commonly preferred implants in cases with sufficient bone stock for fixation (1,3,11,14,16). Although screws are a commonly employed method for the fixation of large fragments, comminution and fragment size may affect implant selection. In instances in which the fracture is too small and comminuted to be fixed, K-wires, washers, and buttress plates may be considered as a potential treatment option (11,17). Nevertheless, it has been proposed that the fracture morphology does not influence the selection of hardware, the size of the hardware, nor the use of washers (11). The dorsal buttress plate is particularly used for comminuted hamate fractures (17,18). This technique has several advantages. Although it provides a more rigid fixation in comminuted fractures, it doesn't fix the CMC joint. It therefore allows an early mobilization. However, it has some complications, including loss of sensation, formation of painful neuroma, and loss of motion due to extensor tendon adhesions or injury. Implant removal may be required due to implant-related pain (17).

In the current study, the most commonly used implants were screws for hamate fractures and K-wires for metacarpal fractures. K-wires were removed around the 4th week. Although some authors in the literature recommend that ligament injuries require at least six weeks for healing (19,20), the time required for K-wire removal varies between four and twelve, according to the literature (11,18-21). These injuries often involve a combination of bone and soft tissue injuries. Bone fixation combined with soft tissue repair provides significant stability. Furthermore, no loss of reduction or residual instability was observed in relation to the timing of K-wire removal in the present study. It is important to note that prolonged K-wire fixation can have a negative impact on hand movement (21). Therefore, it is not necessary to adopt overly aggressive approaches. No complications or reoperations were experienced in the current series. Although pain, stiffness, decreased grip strength, CMC subluxation, arthritis, malunion, nonunion, avascular necrosis, and nerve injury have been defined as complications in the literature, such complications are rare (1,4,11). Furthermore, they can be frequently aggravated by delayed diagnosis or inadequate rehabilitation (4,7,8). Although the current study demonstrated that delayed diagnosis was more likely to result in post-traumatic osteoarthritis, the current study has demonstrated that the difference was not statistically significant (Table 4).

HMFD usually has good prognosis and functional outcomes (1,3,11,14). However, comminuted fracture, post-traumatic deformity, and delayed diagnosis lead to poor outcomes (3,22). The results of the current study are similar to those of the literature. Cases performed open reduction had worse DASH score and delayed diagnosed cases lower grip strength.

Similar to the current study, it has been shown that patients with HMFD have a decrease in work activities (21). Furthermore, the current study revealed that hand intensive workers experienced greater difficulties in working and returning to work than others.

Study Limitations

This study's main limitation is its retrospective design. Furthermore, the sample is heterogeneous regarding treatment and injury configurations. However, it is one of the largest case series in comparison to the number of cases in the literature. Additionally, this is the first time comprehensive analyses, such as assessments of the impact of injury on RTW, have been performed.

CONCLUSION

HMFD are very rare injuries with a high probability of being overlooked. Missed and delayed diagnosis will lead to functional disability in the hand, chronic pain, arthrosis and medico-legal problems. In cases of severe pain focusing on the hamatometacarpal joint following suspected trauma, the HMFD should be keep it mind and the most appropriate fixation technique for each injury should be planned.

Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Antalya Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (decision number: 3/9, date: 21.03.2024).

Informed Consent: This study was conducted in accordance with the tenets of the Declaration of Helsinki, and informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: H.M., B.A., Concept: M.Ü., B.A., Design: H.M., B.A., Data Collection or Processing: M.Ü., H.H.H., C.H., H.M., Analysis or Interpretation: M.Ü., H.M., Literature Search: M.Ü., H.H.H., C.H., Writing: M.Ü., H.H.H., C.H., B.A.

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