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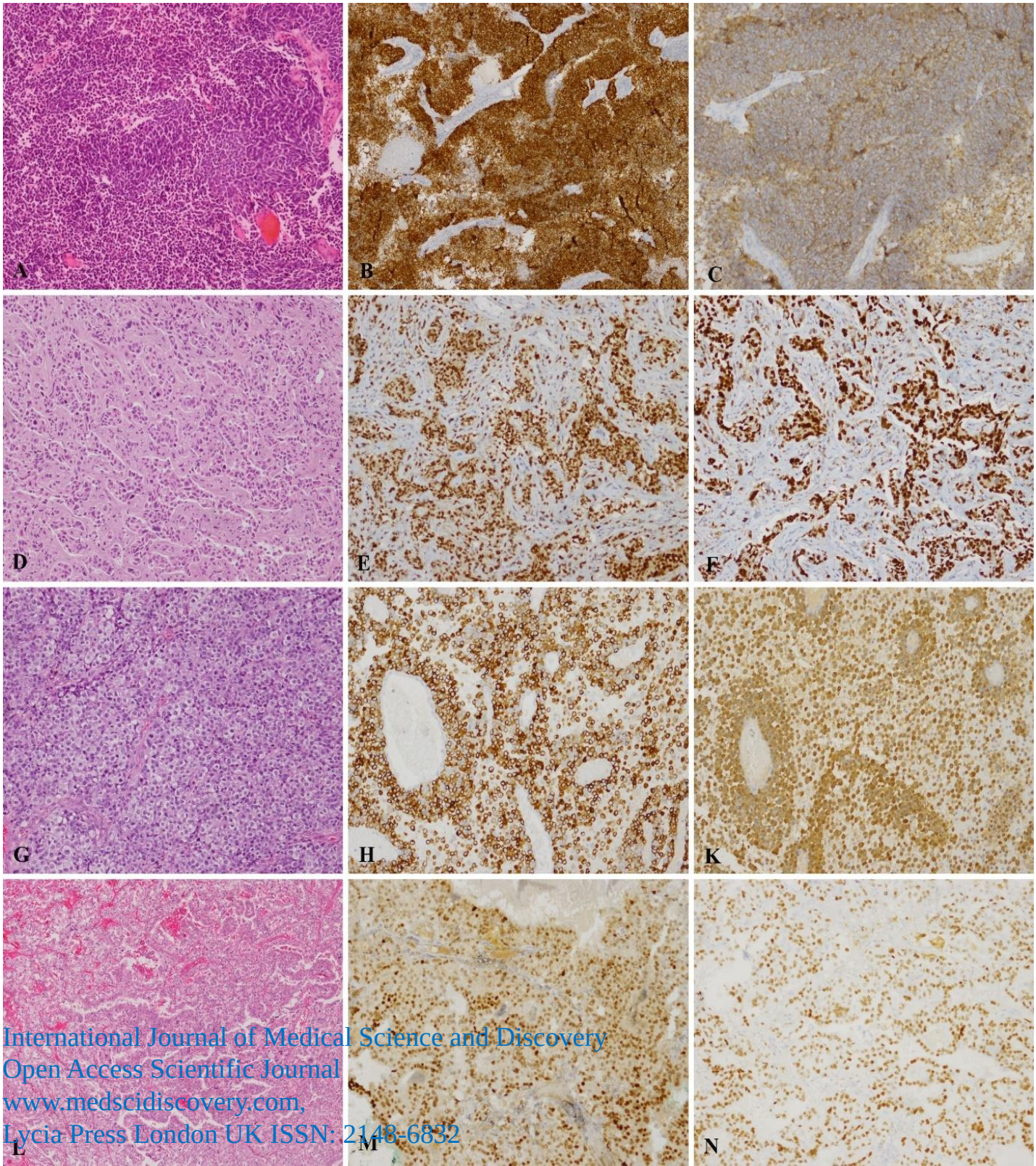

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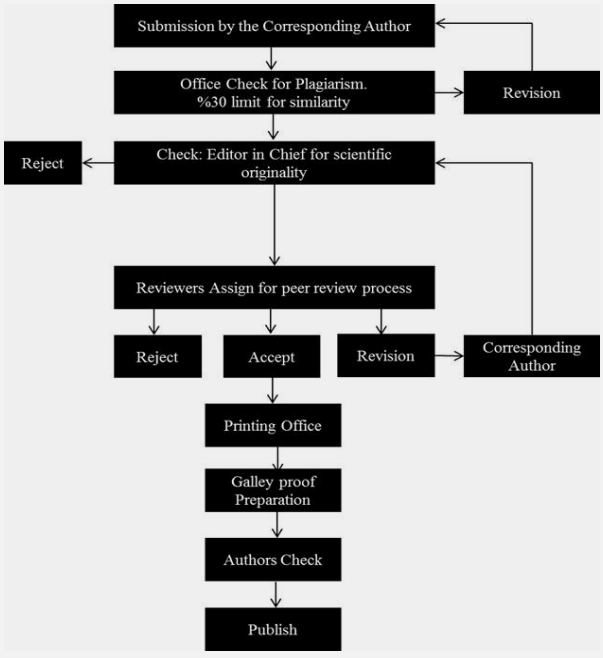

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Zinc levels in Beta-Thalassemia Major: A Review of the Literature

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ABSTRACT

Objective: Zinc is an essential trace element for the body that is involved in various significant body functions such as protein synthesis, DNA synthesis, and cellular growth. It is found in almost every cell and plays an important role in the immune system, affecting both innate and acquired immunity. Patients with beta-thalassemia major are at risk of zinc deficiency. Beta-thalassemia major is an inherited disease caused by a reduction or complete absence of beta-globin chains and the affected patients need repeated blood transfusions to survive. Accordingly, it causes oxidative stress and tissue damage, alteration of antioxidant enzymes, and changes in other essential trace element levels due to iron overload. Zinc levels in beta-thalassemia major patients were reported to be significantly reduced in most of the studies. Serum zinc levels of the patients with beta-thalassemia major should be monitored regularly and zinc supplementation should be provided to these patients.

Keywords: Zinc, Beta-Thalassemia Major, Thalassemias, Review

INTRODUCTION

Zinc is an essential trace mineral, which is crucial for all living tissues, both as a structural component of proteins and because of its important role as a cofactor in enzyme catalysis. Zinc is actively involved in many metabolic activities in the human body such as protein synthesis, DNA synthesis, cellular growth, wound healing, and fertility. The importance of zinc in human body metabolism has been demonstrated by the consequences of zinc deficiency, such as impaired wound healing, reduced immune response, growth retardation, affected bone mineral density, impaired glucose tolerance, neurological disturbances, irritability, and deformed nails (**1**).

Zinc is found in high concentrations in animal products such as meat, fish, and egg and especially in seafood such as mussels. Zinc, which should be taken in a certain amount every day for optimal health, is found in all organs, tissues, and body fluids. Zinc plays a role in the functions of more than 300 metalloenzymes and transcription of more than 2000 genes involved in lipid, protein, and nucleic acid metabolism. It is well known that zinc is essential for many functions of the natural and acquired immune system against pathogens and tissue damage, and has a protective effect against the damages of free oxygen radicals (**2**).

The absorption of zinc takes place actively in the intestine, especially in the duodenum. Its maximum absorption occurs in the middle jejunum and ileum. Zinc is absorbed by enterocytes and goes through the bloodstream. There are special zinc carrier proteins that transport zinc into and out of the cell (**3**). About 80% of the zinc that passed into the plasma is bound to albumin, which functions as a major zinc carrier. Alfa-2 macroglobulin is also another important zinc-binding protein. Zinc, binds to albumin and alfa-2 macroglobulin and can pass through the liver, spleen, kidney, bone marrow, and erythrocytes, where its metabolism will occur rapidly. Excretion of zinc, which can pass into all fluid and membrane structures, is mainly through the feces, then bile, and renal route (**4, 5**).

Review Article

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Beta-thalassemia major

Beta-thalassemia major is an autosomal recessive inherited disease that causes a severe clinical picture characterized by the absence or scarcity of the beta-globin chains of hemoglobin due to homozygous or double heterozygous mutations, excess alpha globin chains in erythrocytes, and imbalance in chain ratios. The incidence of the disease increases with consanguineous marriage (**6**). The severe imbalance of globin chain synthesis causes ineffective erythropoiesis, hemolysis, and anemia. Patients with beta-thalassemia major often have severe transfusion-dependent anemia. Transfusion therapy, which is the mainstay of treatment, allows normal growth and development and suppresses ineffective erythropoiesis, but leads to iron excess (**6, 7**). Excess iron causes oxidative damage and tissue siderosis. Iron overload causes various complications, including diabetes, hypothyroidism, hypogonadism, heart failure, short stature, and liver cirrhosis (**8, 9**). Complications related to iron overloads, such as liver cirrhosis and heart diseases are the leading causes of morbidity and mortality in patients with transfusion-dependent beta-thalassemia major. Therefore, the main treatment strategy is; providing transfusion, reducing the iron burden, and increasing the life expectancy of these patients.

Iron chelation therapy

Iron chelation therapy is a lifelong requirement for patients with beta-thalassemia major (**10**). Iron-binding agents desferrioxamine, deferiprone, and deferasirox are used in treatment to prevent iron accumulation (**11**). However, iron chelating agents also eliminate various other essential elements, including zinc. Desferrioxamine has zinc binding affinity and increases urinary zinc elimination and hyperzincuria, resulting in gradual zinc depletion and growth disturbances, among other symptoms (**7, 12**). Chelation rapidly reduces liver iron, serum ferritin, and myocardial siderosis. Besides, chelation improves cardiac functions, reverses and prevents endocrine complications, reduces cardiac mortality, and increases survival (**10, 11**).

Zinc deficiency

Zinc deficiency is common in developing countries where food is usually vegetable-based and rarely contains animal products. While zinc is easily absorbed by animal proteins, excessive plant meals lead to decreased zinc absorption due to its binding to phytates (**13, 14**). In such countries, zinc deficiency results in infection-related diarrhea and pneumonia, growth retardation, hypogonadism, increased mortality and morbidity due to impaired immune function (**13, 15**).

Zinc levels in patients with beta-thalassemia major

The relationship between zinc and beta-thalassemia major has been the subject of many studies. However, there are some differences between the results of the studies. Although some studies are reporting that zinc levels are not affected in patients with beta-thalassemia major (**12, 16**), the majority of studies support the decreased levels of zinc in these patients. However, the variation in prevalence among these patients draws attention.

Some studies have reported zinc deficiency in beta-thalassemia major patients with a prevalence of 25% or less. Of these, Kwan et al reported zinc deficiency in only 3 of 68 beta-thalassemia major patients (**17**). In another study, a 10% prevalence of zinc deficiency was reported in patients with thalassemia major (**18**). Sultan et al (**19**) included 63 beta-thalassemia major children aged between 5 and 15 years who had been using desferrioxamine for at least 1 year and reported zinc deficiency (zinc levels <50 µg / dL) in 14 patients with a rate of 22.2%. Besides, they also determined that the rate of zinc deficiency was higher in the male gender and those with a disease duration of more than 10 years. Fung et al (**20**) adopted a cut-off value of <70 mg / dL for zinc deficiency and reported decreased zinc levels in 25% of patients with beta-thalassemia major and low bone density between the ages of 6 and 30.

However, in many studies, zinc deficiency has been reported with a 60% or higher prevalence. Ferdaus et al (**21**) reported low serum zinc levels in 60% of beta-thalassemia patients. In the study conducted by Nidumuru et al (**22**), it was reported that the serum zinc levels of 35 transfusion-dependent beta-thalassemia major pediatric patients between the ages of 5 and 15 years were lower compared to healthy children with similar characteristics. They found serum zinc levels were <60 µg / dL in 65% of the patients (26 patients) and evaluated these cases as hypozincemia. Based on their results, they stated that hypozincemia is common in patients with beta-thalassemia major. Mahyar et al (**23**) measured zinc levels in the serum of 40 patients with beta-thalassemia major under 12 years of age and reported that serum zinc levels of <70ug / dL in 26 (65%) of them, while it was within the reference range in only 14 patients. In the study of Shamshirsaz et al (**24**), 220 cases with thalassemia were studied and the prevalence of zinc deficiency was reported as 79.6%. Tabatabei et al reported that 84.8% of thalassemia major patients were having zinc deficiency. They emphasized that the cause of zinc deficiency in these patients was due to insufficient dietary intake (**25**). In a study conducted in Tehran Thalassemia Center (**26**), zinc deficiency was reported in 85.5% of 131 patients with beta-thalassemia major.

Arcasoy et al (**27**) reported that serum zinc levels were lower in all 30 beta-thalassemia major patients compared to controls. Mashhadi et al (**28**) reported severe zinc deficiency in all cases in their study on 333 transfusion-dependent patients with beta-thalassemia major. There were no cases of normal or increased zinc levels.

Possible reasons for differences between studies

Differences in the number of patients included in the studies, the differences in regular transfusion criteria or the duration of transfusions, the differences in chelation therapy, the use of different drug doses, and the differences in the duration of the disease may be the reason for the different prevalence of zinc deficiency in different studies. Besides, the fact that studies were conducted in regions with different socioeconomic statuses may have caused dietary differences in zinc levels (**29, 30**). Again, as stated in some studies, different zinc cut-

off values draw attention and we believe that different prevalence between the studies may be caused by the different definitions of deficiency.

Beta thalassemia major, zinc, and oxidative stress

Oxidative stress is defined as the disruption of the balance between oxidants and antioxidants in the body due to excessive peroxide and free radical production. Oxidative stress occurs as a result of increased levels of lipid peroxides and free radical intermediates and a decrease in total antioxidant capacity in patients with beta-thalassemia major where frequent blood transfusions are required due to severe anemia (**31, 32**). Increased oxidative stress biomarkers are determined with decreased antioxidant levels in patients with beta-thalassemia major. Iron overload seen in patients with beta-thalassemia major may lead to decreased levels of trace elements such as vitamins and zinc as a result of oxidative stress caused by hemolysis and inflammation (**33, 34**).

The use of iron chelating agents in combination with antioxidants may aid in regulating oxidative status in patients with beta-thalassemia major (**31, 32**). Zinc has important antioxidant properties (**35**). Zinc has a protective role in the formation of free radicals and oxidative stress. Zinc is involved in the structure of superoxide dismutase, an antioxidant-effective enzyme, and metallothioneins that protect tissues from the harmful effects of free radicals (**36**).

Selective administration of essential trace elements such as zinc and antioxidant molecules to reduce the degree of oxidative damage and related complications in beta-thalassemia major may be beneficial in reducing oxidative stress in these patients.

Zinc is not stored by the body, so it is important to eat foods containing zinc every day to avoid deficiency. Zinc is also present in dietary supplements. Intervention strategies to combat zinc deficiency include zinc supplements, food supplements through the addition of zinc additives to food, and dietary alterations (2, 36).

CONCLUSIONS

In conclusion, in the light of the literature review, it is seen that zinc deficiency is present in most of the patients with beta-thalassemia major. Zinc levels were low in most studies. It should be kept in mind that zinc levels may be low in patients diagnosed with beta-thalassemia major who are under follow-up. In beta-thalassemia major patients who are transfusion-dependent and treated with chelators, serum zinc levels should be monitored and prophylactic zinc supplements should be considered in the routine management of these patients.

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Cardiovascular events post cannabis abuse during the COVID-19 pandemic

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ABSTRACT

Objective: The pandemic caused by Sars-CoV-2 (COVID-19) has changed dramatically individuals' life worldwide. The implication of measures of public health protection, the social distance and isolation, the lockdown and the decrease of social life activities caused escalated anxiety, depression, physical inactivity on the one hand and widespread unemployment and financial crisis on the other hand. Preliminary studies during COVID-19 pandemic reported an increase in the use of psychoactive substances, including alcohol and cannabis (CB). The latter has been linked with harmful cardiovascular and respiratory effects (eg. lung cancer, bronchitis and pulmonary emphysema). Especially people with substance use disorders were further stressed by the current circumstances and were found to intensify consumption of cannabinoids (**1-4**). This short review focuses on the possible cardiovascular impact of CB abuse in the era of Covid-19 pandemic. It aims to stress the worldwide clinical attention and the clinicians' awareness on the development of specific prevention and intervention strategies against CB addiction during pandemics.

Keywords: pandemic, psychoactive substances, marijuana, cannabis, cardiovascular, coronary syndrome, myocardial infarct, Sars-CoV-2, COVID-19

INTRODUCTION

The last decades many countries and states have legalized marijuana's (MJ) use and other cannabinoids for medical and recreational purposes. MJ derived from the hemp plant Cannabis sativa is the most commonly abused psychoactive drug around the privileged world and about 11.8 million young individuals in the United States report MJ use with a dramatic increase of consumption rates among all age groups (**5, 6**). Furthermore, nowadays these drugs are even more available and accessible to people stressed by the COVID-19 crisis which results on few systemic acute and long term side effects. Literature data report that serious adverse events of cannabinoids include myocardial infarction (MI), sudden cardiac death, cardiomyopathy, stroke, transient ischemic attack, and CB arteritis, vascular diseases (coronary, cerebral and peripheral), arrhythmias and stress cardiomyopathy to be the less investigated. Many of the victims of these disorders are young men with almost none cardiovascular risk factor. As MJ has become extremely prevalent in our society, the prevention of acute cardiovascular events post MJ use requires collaboration among cardiologists, drug users and addiction experts (**7, 8**).

Cardiovascular effects of cannabinoids (CB)

Physiology

The current available literature associates MJ with several serious adverse cardiovascular disease (CVD) events, due the interaction of cannabinoids with the endogenous endocannabinoid system with different mechanisms like "CB arteritis," CB- induced vasospasms and platelet aggregation (**9, 10**). The French Addictovigilance Network (during 2006-2010) reported that only 2% of all CB related events were proved to be CVD side effects, including mainly acute coronary syndromes and peripheral arteriopathies (**11**).

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Nevertheless, reports associate the increased frequency of MJ use with the risk of cardiac arrhythmias and MI, whereas the chronic cannabinoids use has been directly linked with increased angina frequency, due to a decrease in the angina threshold, diminished sympathetic and parasympathetic nervous system (NS) signal transduction, serum aldosterone increase, central and peripheral vasoconstriction, and hypertension (7). Most of the CVD effects of cannabinoids are mediated through the subsequent activation of the sympathetic NS and the inhibition of the parasympathetic autonomic NS (12). Thus, CB smoking increases the heart rate, the serum norepinephrine level and myocardial oxygen demand immediately, it reduces oxygen supply and leads to pro-coagulant or pro-thrombotic state, while the increased atropine inhibits the parasympathetic activity (12-17). According to recent reports, the CB use might also cause dose-dependent elevation of the systolic blood pressure and heart rate (18, 19) and induce atrial fibrillation shortly after smoking MJ (20). While smoking CB, the oxygen delivery to the heart and other vital organs is diminished and the carboxyhemoglobin levels are elevated, resulting in reduce of the time to onset of symptoms during exercise in patients with stable angina (12).

Complications of MJ abuse

1. **Acute Coronary Syndrome (ACS):** The CB use is found to increase fivefold the risk for ACS within a 5 hours window post abuse, whereas the reintroduction of MJ abuse is directly correlated with recurrence of the syndrome (12, 21), and this risk dramatically declines after the first hour of exposure to MJ (22, 23). Moreover, these acute MI events are associated with higher short-term mortality in CB users, perhaps due to the analgesic effect of MJ on anginal symptoms (14).

   Several case reports indicate the coronary vasospasm-induced cardiomyopathy as the principal effect of CB abuse (24-29), whereas most of them are patients without CVD history or related risk factors. The majority of these individuals presented at the Emergency Departments with ACS after MJ use, with ST-segment elevation in their Electrocardiogram (ECG) and increased cardiac enzymes and were subjected to cardiac magnetic resonance imaging or coronary angiography which were finally negative for occlusive atherosclerotic disease (12, 21), indicating the coronary vasospasm as the most possible cause of these CVD events (24). Retrospective systematic review of published articles showed ST segment elevation in 60% of EKGs, 36,8% of patients had normal coronary arteries, 35% had LAD coronary artery occlusion and 34% of cases had concomitant cardiomyopathy compared to non-users (30-32).

   In other cases, coronary angiogram revealed occlusive thrombus inside the coronary artery which was attributed to non-reversible platelet aggregation due to CB use (10, 33). The possible mechanism is that the CB use inhibits the parasympathetic system, induces an inflammatory effect in the arterial wall, which leads in endothelial erosion due to oxidative stress, plaque rupture, factor VII activation and finally to thrombus formation (23, 34, 35).

   Also, MJ smoking is proven to decrease the maximum exercise capacity in healthy individuals, while the cutoff of angina threshold is lowered when comparing individuals with MJ smoking and nicotine smoking. The exercise time to angina post MJ smoking is reduced by an average of 48% as compared to 23% after tobacco cigarette smoking, indicating that the increase in cardiac events was independent of tobacco use (22).

   On the contrary, cardiovascular mortality in patients with known CAD is increased by 3-fold especially after MI in MJ users compared to non MJ users (22). A meta-analysis on non-fatal MI related to the CB smoking indicated the MJ abuse as the third-highest-ranking associated variable (Hata! Başvuru kaynağı bulunamadı.).

2. **Left Ventricular Systolic Dysfunction:** Besides, cannabinoids were found to reduce myocardial contractility, whereas this systolic dysfunction might result from persistent tachycardia, atrial fibrillation or ischemia in the case with pre-existing CAD (12).

3. **Rhythm Disturbances and Sudden Cardiac Death:** The most commonly reported arrhythmia post cannabinoids smoking in individuals without cardiovascular history is atrial fibrillation (26%), followed by ventricular fibrillation (22%) and Brugada pattern (19%) (39). Retrospective studies report that the common mortality causes for CB users are different rhythm disturbances (sinus tachycardia, ectopic atrial or ventricular rhythm, and atrial or ventricular fibrillation). Most articles attribute these tachyarrhythmias to a hyperadrenergic state after MJ use (38).

   Adrenergic stimulation causes a reduction in action potential duration and results in a microreentrant tachycardia (17). Serious ventricular arrhythmias shortly after CB smoking may cause dizziness, syncope, cardiac arrest or even sudden cardiac death, due to acute myocardial microvascular spasm, acute MI, or pre-existing CAD (12, Hata! Başvuru kaynağı bulunamadı.).

   Thus, research studies found that MJ use is associated with a three-fold higher mortality rate after MI, with higher mortality rate among CB users with MI compared to non-users (39).

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FLAMSA vs BU-FLU in patients undergoing allogeneic stem cell transplantation for acute leukemia and myelodysplastic syndrome

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ABSTRACT

Objective: Similar to other regimens, the specific role of fludarabine-amsacrine-cytarabine (FLAMSA) regimen before allogeneic transplantation is still unclear. We compared the results of patients who received either the FLAMSA regimen or the busulfan-fludarabine (BuFlu) regimen prior to allogeneic transplantation.

Materials and Methods: Patients who underwent allogeneic transplantation and who administered reduced-intensity conditioning (RIC) regimens before transplantation were included in to the this study. Patients were divided into two groups (BuFlu and FLAMSA) according to the applied RIC regimens.

Results: A total of 37 allogeneic transplant patients (13 FLAMSA, 24 BuFlu patients) were included in this study. The time between diagnosis and transplantation was shorter in the patients in the FLAMSA group compared to the patients in the BuFlu group ($p<0.001$). Although platelet engraftment time was shorter in the FLAMSA group than in the busulfan-fludarabine group ($p=0.048$), the neutrophil engraftment time and adverse events were similar in the two groups (all $p>0.05$). The estimated median disease-free survival of the patients in the FLAMSA group was 7.2 months, while it was 3.7 months in the busulfan-fludarabine group ($p=0.778$). Similarly, the estimated median overall survival of the patients in the FLAMSA group was 7.2 months, while 7 months in the BuFlu group ($p=0.815$).

Conclusion: BuFlu and FLAMSA are two alternative conditioning regimen options that provide similar efficacy, toxicity profile and survival as regimens used in allogeneic transplantation. The FLAMSA regimen may be an alternative to Bu-Flu as a priming regimen for allogeneic stem cell transplantation. Meta-analyzes should be performed to evaluate with more patients.

Keywords: Allogeneic stem cell transplantation; Busulfan; Flamsa; Acute leukemia; Myelodysplastic syndrome

Research Article

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment for several hematological diseases. Reduced-intensity conditioning (RIC) regimens were created to decrease the adverse events related to the myeloablative conditioning (MAC) regimen, particularly in elderly and fragile patients (1). However, subsequent studies revealed that RIC regimens were remarkably associated with the risk of relapse (2). Although non-relapse mortality (NRM) appears to be lower with RIC regimens as compared to MAC regimens, since AML includes a group of chemosensitive diseases, increasing concerns that RIC preparative regimens may have a negative impact on the risk of relapse (3). The archetype RIC protocol comprises reduced-dose busulfan-fludarabine (BuFlu). Requested outcomes were obtained using a busulfan-based reduced conditioning regimen in myelodysplastic syndromes (MDS) or secondary acute myeloid leukemia (sAML) (4, 5). Afterward, the efficacy of different dose intensities of busulfan in the combination of fludarabine has also been compared in the trials (6, 7).

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In the early 2000s, alternative conditioning regimens have been developed (8). In the beginning, the combination of fludarabine, amsacrine, and cytarabine (FLAMSA) was adopted for high-risk MDS and AML patients to unite advanced anti-leukemic effect with the usefulnesses of RIC regimen (9, 10). Recently, in a study of 265 patients with intermediate or poor-risk AML patients using FLAMSA-RIC as a conditioning regimen before HSCT, promising outcomes with 2-year disease-free survival (DFS) of 52.8% and overall survival (OS) 56.1 were obtained (11). There are limited trials that comparing FLAMSA-RIC with other frequently utilised RIC regimens (12, 13). For this reason, we compared the results of AML-MDS and acute lymphoblastic leukaemia (ALL) patients who received either the FLAMSA regimen or the BuFlu regimen before transplantation.

MATERIAL and METHODS

Patients who underwent allogeneic HSCT between 01.01.2014 and 31.12.2020 due to the diagnosis of AML, ALL or MDS and who administered RIC regimens before transplantation were included in this study. RIC regimens were applied to the patients because of advanced age, presence of comorbidity or poor performance status. Patients were divided into two groups (BuFlu and FLAMSA) according to the applied RIC regimens. Information such as age, gender, diagnosis, donor types, used conditioning regimens, and lifespan of the patients were retrospectively analysed from electronic patient records. In addition, neutrophil engraftment (the first day when the neutrophil count was over 500/mm^3 for three consecutive days) and platelet engraftment times (the first day when the platelet count was around 20000/mm^3 for three consecutive days) of patients were calculated. Graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) diagnoses were made according to determined international criteria (14, 15). Adverse events due to BuFlu or FLAMSA conditioning regimens were defined and classified according to the Common Terminology Criteria for Adverse Events version 5.0.

The scheme of administration of the BuFlu regimen is as follows: fludarabine 30 mg/m2 intravenously daily between days -6 and -2, and busulfan 3.2 mg/kg intravenously daily on day -3 and -2.

The administration of the FLAMSA regimen is as follows: fludarabine 30 mg/m2 daily, cytarabine 2 g/m2 daily, amsacrine 100 mg/m2 daily. All drugs were administered intravenously for 4 days between -10 and -7 days. All patients were infused with peripheral blood-derived stem cells obtained from donors via G-CSF on day 0.

Our study was conducted under the ethical standards, and approval was obtained from the Inonu University Health Sciences non-interventional ethics committee before starting the study (decision no: 2021/1815).

Statistical analysis

Normality analysis of quantitative data such as age, the time between diagnosis and transplantation, and engraftment times was performed using the Shapiro-Wilk test. Independent samples t-test was used to compare the mean age between the BuFlu and FLAMSA groups, and the Mann-Whitney U test was used to compare other quantitative data. Chi-square test was used to compare categorical data such as gender, diagnosis, comorbidity and adverse event incidences between BuFlu and FLAMSA groups. A Log-rank test was performed to compare DFS and OS of patients who received BuFlu or FLAMSA as a regimen.

RESULTS

A total of 37 allogeneic transplant patients (13 FLAMSA, 24 BuFlu patients) were included in this study. The initial patient characteristics before transplantation are summarised in Table 1. All patients had a complete response to the treatments before allogeneic transplantation. The time between diagnosis and transplantation was shorter in the patients in the FLAMSA group compared to the patients in the BuFlu group ($p<0.001$).

Table 1. Initial characteristics of two groups who underwent allogeneic transplantation

	Busulfan-fludarabine (n=24)	FLAMSA (n=13)	p value
Age, mean±SD	58.1±7.4	54.6±8.5	0.199
Gender			
Male, n	19 (79.2%)	8 (61.5%)	0.275
Female, n	5 (20.8%)	5 (38.5%)	
Disease			
AML, n	17 (70.8%)	12 (92.3%)	0.272
ALL, n	3 (12.5%)	0 (0%)	0.637
MDS, n	4 (16.7%)	1 (7.7%)	0.631
Comorbidity			
Present, n	17 (70.8%)	5 (38.5%)	0.118
Absent, n	7 (29.2%)	8 (61.5%)	
ECOG performance scale			
1, n	3 (12.5%)	1 (7.6%)	1
2, n	17 (70.8%)	6 (46.2%)	0.261
3, n	4 (16.7%)	6 (46.2%)	0.123
Donor type			
MRD, n	19 (79.2%)	12 (92.3%)	0.394
MUD, n	5 (20.8%)	1 (7.7%)	
Time between diagnosis and transplantation, median (day)	40 (27-62)	41 (22-85)	0.345
Number of CD34+ cells given before transplantation, median	7.29x10^6/kg (5.11x10^6/kg-12.15x10^6/kg)	7.93x10^6/kg (4.6x10^6/kg-11.7x10^6/kg)	0.681

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The neutrophil engraftment times, platelet engraftment times, acute and chronic GVHD rates of the two groups, and adverse events in the early period after transplantation are given in table 2. None of the patients developed pulmonary or central nervous system toxicity. Although platelet engraftment time was shorter in the FLAMSA group than in the busulfan-fludarabine group (p=0.048), the neutrophil engraftment time, GVHD and SOS rates, and adverse events were similar in the two groups (all p>0.05).

Fifteen (62.5%) of the patients in the BuFlu group died after a median follow-up of 5.5 (1-48.8) months. Eight (61.5%) of the patients in the FLAMSA group died after a median follow-up of 7.2 (1-37.9) months. Although the median follow-up times of the two groups were different, no statistically significant difference was observed between the groups (p=0.448).

Of the patients in the BuFlu group, 5 (33.3%) died from infection, 3 (20%) from relapse, 6 (40%) from organ failure due to GVHD, and 1 (6.7%) from organ failure due to SOS. Of the patients in the FLAMSA group, 5 (62.5%) died from infection, 1 (12.5%)from GVHD-related organ failure and 2 (25%) from SOS-related organ failure.

The estimated median DFS of the patients in the FLAMSA group was 7.2 months, while it was 3.7 months in the busulfan-fludarabine group, but no statistically significant difference was observed between the groups (p=0.778) (Figure 1). Similarly, the estimated median OS of the patients in the FLAMSA group was 7.2 months, while it was 7 months in the BuFlu group, but no statistically significant difference was observed between the groups (p=0.815) (Figure 2).

Table 2: Comparison of the clinical outcomes and adverse events of the two groups

	Busulfan-fludarabine (n=24)	FLAMSA (n=13)	p value
Neutrophil engraftment time, median (day)	16 (11-21)	16 (11-20)	0.732
Platelet engraftment time, median (day)	15.5 (10-28)	13 (13-15)	0.048
Febrile neutropenia, n	17 (70.8%)	10 (76.9%)	1
CMV reactivation, n	14 (58.3%)	7 (53.8%)	1
BK virus reactivation, n	7 (29.2%)	5 (38.5%)	0.716
Creatinine elevation, n	3 (12.5%)	2 (15.4%)	1
Liver enzyme elevation, n	5 (20.8%)	3 (18.8%)	1
Arrhythmia, n	1 (4.2%)	0 (0%)	1
SOS, n	11 (45.8%)	6 (37.5%)	0.747
Acute GVHD, n	5 (20.8%)	1 (7.7%)	0.394
Chronic GVHD, n	3 (12.5%)	3 (23.1%)	0.643

CMV: Cytomegalovirus, **SOS:** Sinusoidal obstruction syndrome, **GVHD:** Graft versus host disease

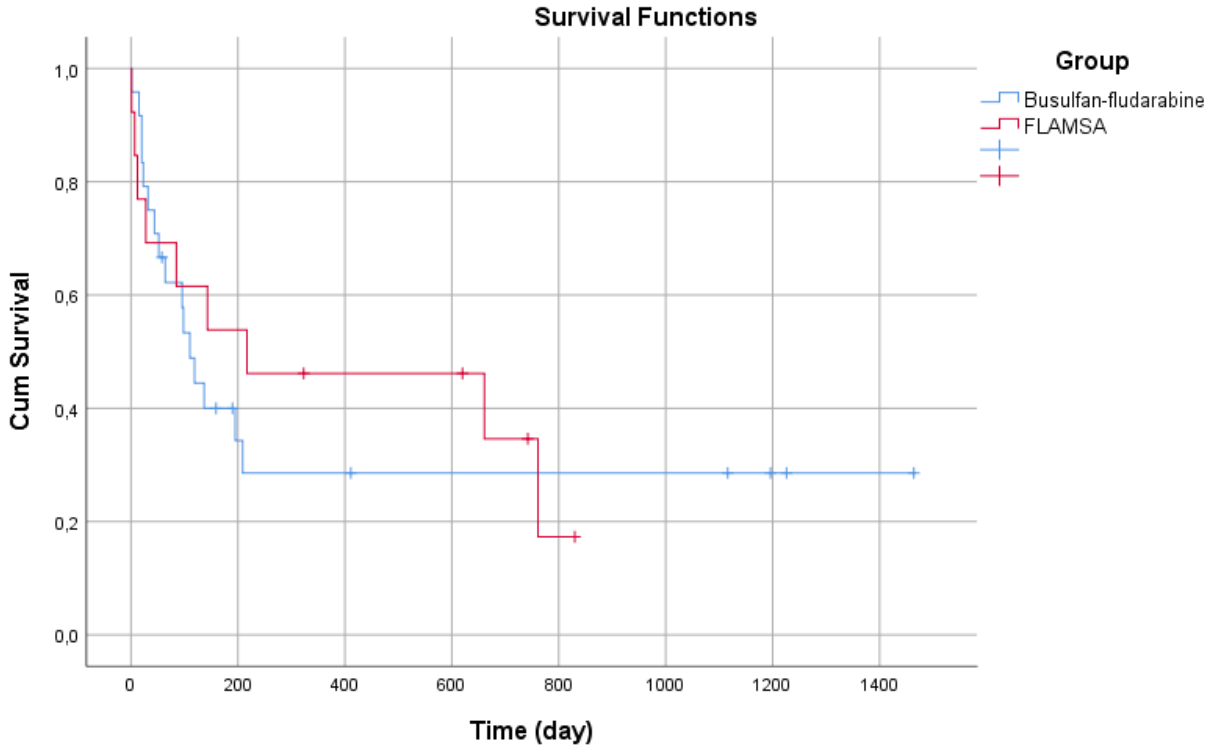

Figure 1: Disease-free survival of two groups

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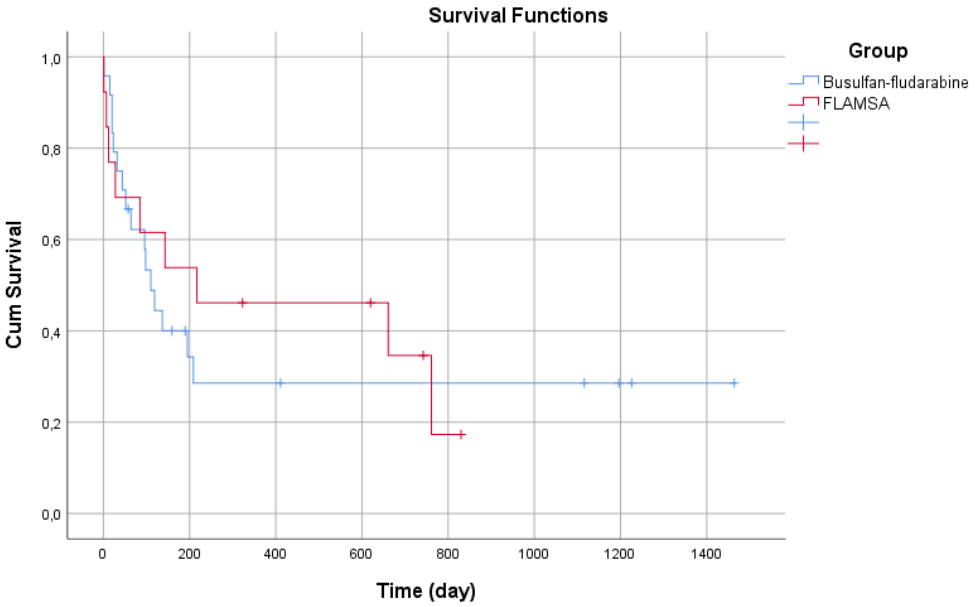

Figure 2. Overall survival of two groups

DISCUSSION

Data on the option of the conditioning regimen for patients who underwent allogeneic HSCT is limited (13). We compared the consequences of two frequently utilised conditioning regimens, namely BuFlu and FLAMSA regimen, in this study. No remarkable difference could be noticed in regard of DFS, OS, GVHD and SOS. When looking at engraftment times, the time to platelet engraftment was shorter in the FLAMSA group than in the busulfan-fludarabine group (p=0.048). However, there was no difference between the groups regarding the time to neutrophil engraftment (p=0.732). RIC protocols were emerged to decreasing adverse effects and making HSCT suitable for fragile patients. However, RIC protocols may not be sufficiently effective for patients with high-risk characteristics (**16**). FLAMSA-RIC was introduced in 2005 to overcome this restriction (**8**). There is increasing evidence from studies that non-relapse mortality is lower after RIC regimens than after MAC regimen (**17**). However, Scott et al. demonstrated that RIC regimens had been associated with a higher relapse rate (51% vs. 15.9%, respectively) compared with MAC regimens. Also, OS was remarkably better with MAC rather than RIC (**18**). The RIC conditioning regimen BuFlu has appropriate tolerability, and Rambaldi et al. demonstrated that even the BuFlu MAC regimen (Busulfan total dose: 12.8 mg/kg) associated with lower 1-year nonrelapse mortality rather than busulfan/cyclophosphamide (17.2% vs. 7.9%) According to the results of this trial, the BuFlu regimen can be selected when potent antileukemic activity is desired in groups for which consideration of adverse effects related to the treatment regimen is a priority (fragile and/or older patients) (**19**).

Chen et al. compared two different busulfan doses-BuFlu regimens (3.2 mg/kg vs 6.4 mg/kg) in AML and MDS patients. Two-year DFS and OS were also similar between both regimens. Two-year NRM rates were identical for both regimens (**6**). Shimoni et al. compared BuFlu MAC regimen (FB4, total busulfan dose 12.8 mg/kg) and BuFlu RIC regimen (FB2, total busulfan dose 6.4 mg/kg) in patients with AML and MDS. Shimoni et al. found that NRM and OS rates were similar in both conditioning regimens (**7**).

Heinicke et al. found that FLAMSA-TBI resulted in decreased relapse incidence, rather than BuFlu conditioning regimen, according to multivariate analysis (p=0.04). Also, a better DFS rate was observed FLAMSA-TBI regimen group compared with BuFlu group. In univariate analysis, NRM was 16.1%, 16.4%, and 26.7%, in the BuFlu, FLAMSA-Total body irradiation (FLAMSA-TBI), and FLAMSA-Bu groups, respectively (p<0.01). However, no statistically significant result was demonstrated between the groups regarding 2-year OS. The incidence of grade II-IV acute GVHD is higher in the BuFlu group than in the FLAMSA-TBI group (21.1% vs 26.9%, p<0.001). However, there was no difference between the groups in terms of the incidence of chronic GVHD (**12**).

In a study, treosulfan-based regimen compared to BuFlu plus thiotepa or FLAMSA-RIC as conditioning regimen for AML patients no difference was observed with regards to NRM, DFS, OS rates. Likewise, GVHD rates similar between all groups (**13**). These results contradict the argument that the development of chronic GVHD is associated with busulfan-induced prolonged dysfunction of anti-infectious immunity (**20**).

The limitations of this trial are related to the retrospective nature of the study. At the same time, the limited number of patients included in this trial is among the limitations of our research.

CONCLUSIONS

BuFlu and FLAMSA are two alternative conditioning regimen options that provide similar efficacy, toxicity profile and survival as regimens used in allogeneic transplantation. Conflicting results were obtained in trials comparing the endpoints (OS, PFS, NRM) of BuFlu and FLAMSA-RIC. Meta-analyzes should be performed to evaluate with more patients.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Mean Platelet Volume increase in Endometriomas and Benign Ovarian Cysts: A prospective case-controlled study

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ABSTRACT

Objective: The aim of this research is to compare mean platelet volumes (MPV) among women with ovarian endometriomas, women with benign ovarian cysts and infertile women who were otherwise healthy.

Material and Methods: Women were selected for the ovarian endometrioma and benign ovarian cyst group after laparoscopic ovarian cyst excision and confirmed histopathologic evaluation. The control group was assigned from women with male partner infertility or unexplained infertility but who were otherwise healthy. Mean platelet volume calculated as a part of complete blood count, which collected in potassium ethylenediaminetetraacetic acid tubes

Results: There were 98 women in the endometrioma group, 94 in the benign cyst group and 99 in the control group. Mean platelet volume was different among the groups ($p<0.01$). The mean platelet volume in the infertile group was statistically different than in the endometrioma and benign cyst groups and was similar between the endometrioma and benign cyst groups. When compared with the infertile group, the area under the curve and predictive value of the mean platelet volume for the endometrioma and the benign cyst group were 0.73 ±0.03 fl ($p<0.01$, CI 0.65-0.80) and 0.72±0.06 fl ($p<0.01$; CI 0.64-0.79), respectively. Mean platelet volume had a sensitivity of 74% and specificity of 63% for endometrioma and sensitivity of 72%, and specificity of 63% for benign cysts at a cut-off point of 9.05 fl.

Conclusion: The present study demonstrated that mean platelet volume was increased in women with ovarian endometriomas and benign cysts and showed predictive values for endometriomas and benign ovarian cysts.

Keywords: Mean platelet volume, endometrioma, ovarian benign cyst, sensitivity, specificity

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INTRODUCTION

Platelets are blood products without a nucleus that are produced by megakaryocytes in the bone marrow and then released into the bloodstream. It has long been known that the main function of platelets is to stop bleeding from injured vessels. Recent studies have reported that platelets are multifunctional and are the first blood products to accumulate at the site of an injury (**1**). Platelets participate in a variety of tasks to maintain an individual's health, including hemostasis, inflammation, immune response, complement system activation, microbial host defense, angiogenesis, the metastatic process, wound healing and remodeling (**1, 2, 3**). Since the discovery that platelets are multifunctional, many studies have been performed to evaluate whether platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW) have value in disease diagnosis and progression and whether they could be used as prognostic factors (**3,4,5,6**).

In inflammatory conditions, interleukins, including interleukine-1 (IL-1), interleukin-3 (IL-3), interleukin-6 (IL-6), and engrossing tumor factor -α (TNF-α), are released into the bloodstream. Interleukins activate platelets, and activated platelets became larger, which leads to increased MPV. Interleukin-6 has a dual action: first, it may stimulate the liver to produce thrombopoietin, which in turn stimulates megakaryocytes to produce to young platelets; second, IL-6 directly stimulate the megakaryocytes, leading to the production and release of young platelets, which have a high cytoplasmic volume and more granular particles. Both of these action results in an increase of MPV (**7, 8**). When platelets are activated as part of the immune response, they release inflammatory mediators, which leads to the aggregation of immune cells in the inflamed area (**7**). Immune cells in the inflamed area also release inflammatory mediators, leading to enhanced platelet production and activation and an increase of MPV. Based on the knowledge that MPV is affected during inflammatory conditions, MPV has been studied and evaluated as a marker for inflammatory diseases such as ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, and acute pancreatitis **(9, 10**). The results of these studies suggest that MPV could be used as an inflammatory marker in various diseases (**7,11,12,13**). In light of this knowledge, we conducted a prospective study to compare MPV in patients with endometriomas, patients with Benign ovarian cysts (BOC) other than endometriomas, and patients without ovarian tumour.

MATERIAL and METHODS

This prospective study was conducted between February 2012 and December 2015 at Zekai Tahir Burak Women's Health Education and Research Hospital's Department of Gynecology and Infertility in Ankara, Turkey. The study was approved by the hospital's ethics committee (ethical approval no: 22-02-12/20) and conducted in accordance with the Helsinki Declaration. The written informed consent form was obtained from the participants.

The study comprised three groups: an ovarian endometrioma group, a BOC group, and an infertile but otherwise healthy group as a control. The women in the endometrioma group included patients who presented with pelvic-abdominal pain, and in whom physical examination with ultrasound evaluation in infertility and gynaecology outpatient clinic revealed ovarian cysts that indicated endometrioma. The BOC group included women who presented with complaints of pelvic-abdominal pain or who were incidentally diagnosed during physical and ultrasonographic examinations with ovarian cysts larger than 5 cm in size with an initial diagnosis of a BOC. The patients in both groups underwent laparoscopic cyst excision with pathologic evaluation results reporting benign cysts. The control group included infertile women diagnosed in the infertility clinic with male partner infertility (65 women) or unexplained infertility (34 women) and were otherwise healthy. Women with familial Mediterranean fever (FMF), diabetes mellitus, hyperthyroidism, hypothyroidism, thrombocytopenia, cardiovascular disorders, malignancies, hypertension, peripheral vascular diseases, metabolic diseases, or kidney or liver disease were excluded from the study.

Routine antecubital venous blood samples were obtained from all patients by venipuncture for the laboratory analysis and a complete blood count. The samples were obtained preoperatively in the endometrioma and ovarian cyst group and at the initial evaluation in the infertile control group. Blood samples for the complete blood count (CBC) were placed in potassium ethylenediaminetetraacetic acid (EDTA)–based anticoagulated tubes and were measured by a Beckman Coulter LH 780 Analyzer (Beckman Coulter Inc., USA) within 120 minutes. The platelet count and mean MPV were calculated as part of the routine CBC analysis. The reference range values for the CBC data according to local calibration from our hospital's laboratory were as follows: the MPV was 7.4–10.9 femtoliters (fl), the platelet count was 150–450 $\times 10^3/\mu L$, and the leukocyte count was 4–10.3x$10^3\mu L$.

The SPSS statistical software package (SPSS, version 20 for Windows IBM; SPSS Inc., Chicago, Illinois, USA) was used to perform all statistical calculations. All of the data are expressed as the mean ± SD. A two-tailed p-value < 0.05 was considered significant in all statistical analyses. The comparison of groups were carried out with the one-way analysis of variance (ANOVA) test if the group data was compatible with the parametric test assumptions. If the group data was not compatible with the parametric test assumptions, the comparison of groups were carried out with the Kruskal–Wallis H test. Subgroup analysis was performed with post-hoc tests (Tukey's test for ANOVA, the Games–Howell test for Kruskal–Wallis) in the presence of differences among groups. Comparison of MPV among groups was carried out with the Kruskal–Wallis H test because the distribution of variances is not homogeneous among groups. Receiver operating characteristic (ROC) curves were constructed by plotting the values for MPV. The inflection points for the ROC curves used as cut-off values for the identification of endometrioma and BOC; sensitivity and specificity for cut-off values calculated, and $p < 0.05$ with 95% confidential intervals (CIs) not crossing 1 were considered statistically significant.

RESULTS

The study comprised 291 women, with 98 women in the ovarian endometrioma group, 94 women in the BOC group, and 99 women in the infertile group. The patients' ages, body mass indexes (BMIs), and leukocyte and platelet counts were similar among the groups ($p = 0.45$, $p = 0.33$, $p = 0.18$, and $p = 0.67$, respectively). The MPV was different among the groups ($p<0.01$). Subgroup analyses were performed with the Games–Howell test for MPV. When the endometrioma group was compared with the BOC group, the result was statistically insignificant between the groups ($p = 0.96$). The comparison of the endometrioma group with the infertile group regarding MPV was statistically significant ($p<0.01$). Comparing the infertile group with the BOC group yielded statistically significant results between the groups ($p<0.01$). The characteristics of the groups and the results of the statistical analyses presented in Table 1.

The predictive value of MPV was assessed for both the ovarian endometrioma and BOC groups with ROC curves (Figures 1 and 2, respectively).

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When ROC curves were compared between the endometrioma and infertile groups, the area under the curve was 0.63 ± 0.03, which was statistically significant (p<0.01; 95% CI: 0.54–0.68). The cut-off point for endometrioma in the ROC curve was 9.55 with a sensitivity of 59% and a specificity of 60%.

When the ROC curves were compared between the BOC group and infertile groups, the area under the curve was 0.61 ± 0.03, which was statistically significant (p<0.01; 95% CI: 0.54–0.68). The cut-off point for BOC in the ROC curve was 9.55 with a sensitivity of 57% and a specificity of 59%.

Table 1. The feature of the groups and results of statistical analyses

Features	Endometrioma (n= 98)	BOC (n=94)	Infertility (n=99)	p
Age (year)	29.7±6.7	30.5± 8.1	28.2± 4.7	0.45
BMI kg/m^2	25.8±3.8	26.6±3.7	26.2±4.3	0.33
Leucocytes (x10^3 mm^3)	6.9±1.5	7.1±1.5	7.3±1.5	0.18
Platelets (x10^3 mm^3)	262±57	269±68	269±61	0.67
MPV (fL)	9.9±1.2	9.7±1.3	8.9±0.8	0.00

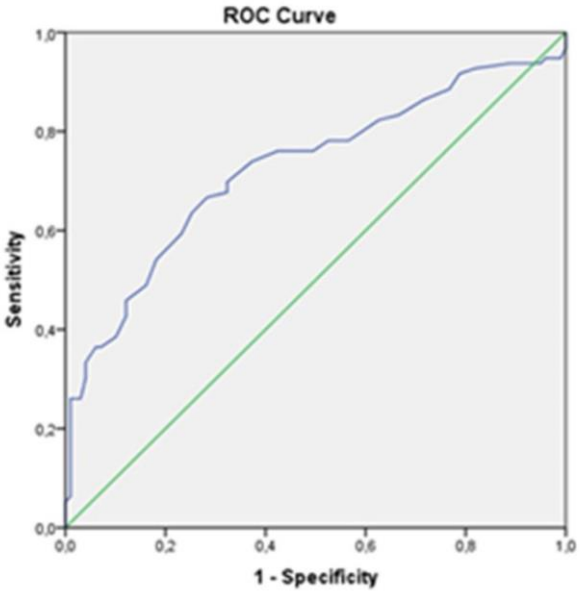

Figure 1. The receiver operator curve of the ovarian endometriomas group.

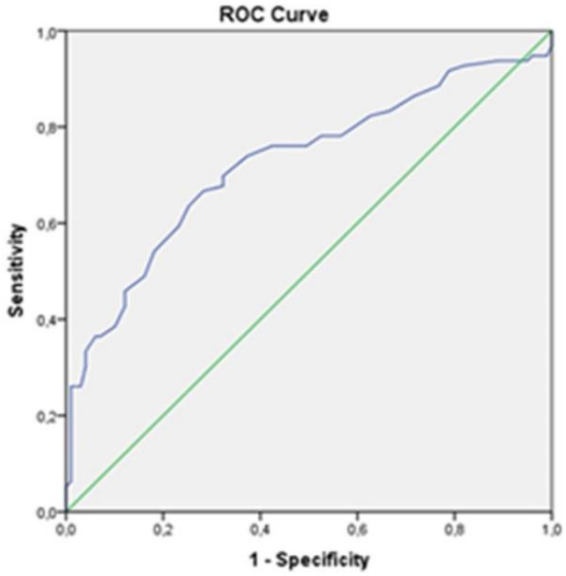

Figure 2. The receiver operator curve of the benign ovarian cyst group.

DISCUSSION

The present study showed that MPV was higher in the patients with endometriomas and patients with Benign ovarian cysts (BOC) than in infertile but otherwise healthy women, and MPV had predictive value for endometriomas and BOC. The increased MPV in patients with endometriomas and BOC can be explained in two ways. First, ovarian cysts apply constant pressure to the ovarian tissue, which causes cells to stretch and atrophy; this leads to the release of inflammatory cytokines and initiates the release of inflammatory mediators, which creates inflammatory conditions in the ovary (**14, 15**). Second, ovarian cysts distort the shape and course of the ovarian arteries, resulting in pressure on the vessels (**16**). Both of these pathways lead to the development of hypoxia in the ovarian tissues. In hypoxic conditions, the ovarian cells release proinflammatory cytokines and chemokines (**17,18**). Inflammation mediators lead to platelet release by megakaryocytes as well as the initiation of platelet activation and the aggregation of platelets in the inflamed tissue. The production of platelets by megakaryocytes and their activation by inflammatory mediators increases platelet volume, which results in an increase of MPV (**2,3,7**).

High-grade inflammatory conditions, such as active rheumatoid arthritis and attacks of FMF, are associated with the circulation of predominantly small platelets due to the rapid consumption of large-size platelets at the inflammatory site (**19**). In contrast, chronic inflammatory diseases are characterized by large-size platelets (and increased MPV) in the circulation (**19**). During a chronic inflammation process, platelet consumption is slow, and inflammatory mediators constantly stimulate platelet release and the activation of platelets, resulting in an increase of MPV. Our study results are in accordance with previous studies and showed that MPV was higher in patients with endometrioma and patients with BOC than in infertile but otherwise healthy women. Endometrioma and other types of BOC are chronic, progressive inflammatory conditions that lead to the constant production of inflammatory cytokines, resulting in the release of a high volume of platelets and the activation of platelets.

Yavuzcan et al. compared MPV among patients with advanced-stage (stage 3/4) endometriosis with endometrioma (OMA), patients with a non-neoplastic adnexal mass other than endometrioma (non-OMA), and control patients. They found that MPV was similar among the groups, and the differences among the groups were statistically insignificant (**20**). On the other hand, in their retrospective study, Turgut et al. compared the level of MPV in patients with endometriosis with the level of MPV in healthy women. They found that MPV was higher in the endometriosis group, and the difference was statistically significant (**21**). Yildirim et al. reported in their clinical research that MPV was not statistically different between patients with ovarian cancer and patients with benign ovarian tumours (**22**). Qin et al. reported that MPV was not statistically different between benign ovarian tumours and the control group, but MPV was lower in patients with ovarian cancer compared with patients with benign ovarian tumours and the control group (**23**). Our study showed that MPV was higher in patients with endometriomas and patients with BOC. In light of the explanation provided above, the differences in the results of these studies have a plausible explanation. Endometriomas and BOC cause chronic hypoxic conditions in the ovary by exerting constant pressure on the ovarian tissue as well as pressure and distortion of the ovarian vessels. In hypoxic conditions, ovarian cells such as endothelial cells and fibroblasts could release hypoxic-ischemic factor (HIF) (**18**). HIF initiates inflammatory cytokine synthesis and releases cytokines into the blood circulation. Inflammatory cytokines stimulate the production of young, high-volume platelets by megakaryocytes and activated platelets in the bloodstream. Together, these processes result in an increase of MPV in the bloodstream.

CONCLUSIONS

In conclusion, the present study demonstrated that MPV was higher in both endometriomas and BOC and had predictive value. MPV calculated as part of a CBC, which is simple and inexpensive. When the cut off value is determined as 9.55 fl, MPV can be used as a marker in patients with endometriomas and patients with BOC. Although our study shows that MPV is an important biomarker in the diagnosis of endometriomas and BOC. Our findings should be supported by further studies.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

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Possible transmission of Covid-19 infection among healthcare professionals; first defense to early wave of the pandemic

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ABSTRACT

Objective: Healthcare professionals play an essential role in the COVID-19 pandemic on the front lines. There have been a limited number of publications and national status reports on COVID-19 infected healthcare professionals. We aimed to determine the factors that play a role in transmitting COVID-19 infection to healthcare professionals.

Material and methods: Among healthcare professionals, those evaluated as a possible COVID-19 case and whose Polymerase Chain Reaction (PCR) tests were studied in our Emergency Service and Employee Health Polyclinic were included in the study. Age, gender, task, unit, working in COVID-19 units, Thorax Computerized Tomography (CT) and PCR test result, hospitalization status, suspicious contact, and appropriate use of personal protective equipment (PPE) in the work environment and social environment were investigated.

Results: A total of 369 cases were included in the study. 54.7% (n = 207) of potential COVID-19 healthcare professionals worked in COVID-19 units, 22.5% (n = 83) had PCR positive. Employee groups with the highest PCR positivity rate were security guards (88.9%), cleaning staff (31.6%), doctors (26.3%) and nurses (18.8%), respectively. When contact histories with COVID-19 infection were examined; 46.3% of the cases had in-hospital social contact (PCR positivity rate 21.6%), 39.6% had a history of contact with COVID-19 patients (PCR positivity rate 11%). It was determined that 3.3% of the cases (n = 12) were treated in the COVID-19 service, 0.3% (n = 1) was hospitalized in intensive care, 26% (n = 96) were isolated at home, and 70.5 % (n = 260) continued to work. All of the participants were discharged after treatment and returned to their duties.

Conclusion: Adequate training should be given to healthcare professionals to protect them against COVID-19 infection. Additionally, healthcare professionals should show the care to prevent infection in social areas inside and outside the hospital as well as at contact points with patients.

Keywords: COVID-19; pandemic, employee health; infection; healthcare professionals

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INTRODUCTION

The new type of coronavirus infection, named COVID-19 by the World Health Organization (WHO), has spread rapidly, first in China and then all over the world, causing a pandemic. There have been 13 million confirmed cases and approximately 568000 deaths associated with this infection (**1**). Healthcare professionals play an important role in the COVID-19 pandemic by providing care to patients on the front lines. Despite infection prevention and control measures, 22073 cases of COVID-19 among healthcare professionals from 52 countries have been reported to WHO as of 8 April 2020. Due to the fact that infected healthcare professionals are not systematically reported to WHO by governments, the actual number is unknown (**2**). There have been a limited number of publications and national status reports on COVID-19 infected healthcare professionals. More than 3,000 cases have been reported in 422 medical facilities by the Chinese Center for Disease Control and Prevention (**3**). In Italy, currently, 29735 (12.2%) infected healthcare professionals have been reported out of a total of 243000 COVID-19 cases (**4**).

According to US Center for Disease Control and Prevention data, 9,287 (19%) of 49,370 COVID-19 patients diagnosed between February 12 and April 9, 2020 were healthcare professionals, and 27 deaths were reported (5).

In Turkey, the first COVID-19 case was diagnosed on March 11, 2020. Although the number of infected healthcare professionals was not officially announced, it was reported by the Minister of Health on 29 April 2020 that 7428 out of about 1 million healthcare professionals were infected with COVID-19, and the rate of the total number of cases diagnosed with COVID-19 was approximately 6.5% (6). This study has been planned as there are not enough studies about COVID -19 infected healthcare professionals both in our country and worldwide.

In our study, it was aimed to determine the factors that play a role in the transmission of COVID-19 infection to healthcare professionals in our hospital, which operates as a pandemic hospital.

MATERIAL and METHODS

In this study, healthcare professionals of all age groups of both genders who presented to the emergency department in the first one month period of pandemic with COVID-19 symptoms due to a possible contact with COVID-19 positive patient and whose Polymerase Chain Reaction (PCR) tests were studied by taking a combined nose and throat swab sample were included. The age, gender, duty, unit, working status in hospital units specialized for COVID-19, Thorax Computerized Tomography (CT) results, hospitalization status and clinical follow-up were analyzed retrospectively from the patient files in the hospital automation system. Patients whose study data could not be reached and those who were pregnant were excluded from the study. The subjects were contacted by phone and the suspicious contact point, if any, and the proper and necessary use of personal protective equipment in the work and social environment were questioned. PCR test results of the patients were examined from the Public Health Management System Tracking Module of the Ministry of Health.

Whether the healthcare professionals appropriately used the recommended personal protective equipment (PPE) customized for hospital use for fighting against COVID-19 in the unit was evaluated in accordance with the recommendations of the Ministry of Health COVID-19 Infection Guide dated 13.04.2020 (Table 1) and the risk levels of cases were identified (Table 2).

Statistical analysis

The data were analyzed using the SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) computer program. Categorical variables were expressed as numbers and percentages (%), while continuous numerical variables were expressed as mean ± standard deviation (minimum - maximum). Kolmogorov-Smirnov test used for the normality distribution of the data. Chi-square and Fisher's exact tests were used to analyze whether there was a relationship between categorical variables. P <0.05 was considered statistically significant.

Ethics statement: The present study protocol was reviewed and approved by the Institutional Ethical Review Board of our academic hospital (2011-KAEK-25 2020 / 05-13) and the permissions taken from Rebuplic of Turkey the Ministry of Health, General Directorate of Health Services.

RESULTS

The study was conducted in Bursa Yuksek Ihtisas Training and Research Hospital, which has 1520 beds and serves the 4th largest city of Turkey has 3 million inhabitants. A total of 3829 personnel, including 722 doctors, 1776 nurses, 652 cleaners, 216 security guards, 382 office workers, 20 pharmacists, and 61 management services employees, work in the hospital.

A total of 369 cases were included in the study. 65.3% (n = 241) of these cases were females and the median age was 32 (minimum = 20, maximum = 62) years. While 53.4% (n = 197) of the cases were nurses, 20.6% (n = 76) were doctors (Table 3).

It was determined that 54.7% (n = 207) of potential COVID-19 healthcare professionals worked in COVID-19 units. When the use of PPE during risky contact in the units against COVID-19 was examined, it was found that 7.9% (n = 29) of the cases did not use any PPE, and 28.5% (n = 105) only used a surgical mask. It was identified that 95.9% of the cases (n = 354) did not use any protective equipment in social areas such as the recreation room used by healthcare personnel in the hospital. When the risky contact histories in terms of COVID-19 infection were examined, 46.3% (n = 171) of the cases had a history of in-hospital social contact, while the rate of those with a contact history with a COVID-19 infected patient was 39.6% (n = 146). High-risk contact was found in 89.7% (n = 331) of the cases (Table 3).

The PCR results of 77.5% (n = 286) of the cases were negative whereas 22.5% (n = 83) were found to be positive. When the Thorax CT examinations of the cases were evaluated according to the Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19 classification (7), 89.2% (n = 329) of the cases did not have any findings in Thorax CT, while 5%, 7 (n = 21) had typical CT findings and 5.1% (n = 19) had atypical CT findings. When the outcomes were examined, 3.3% (n = 12) of the cases were treated in the COVID-19 service, 0.3% (n = 1) was hospitalized in intensive care, 26.0% (n = 96) were isolated at home, and 70.5% of the participants (n = 260) continued to work (Table 4).

A statistically significant correlation was found in the Chi-square analysis performed to determine the relationship between the positive PCR results of the cases and working status in COVID-19 unit (p = 0.001), appropriate PPE use in COVID-19 areas (p = 0.000), use of PPE in in-hospital social area (p = 0.028), role of healthcare professionals (p = 0.000), contact history (p = 0.000), and the type of PPE used (p = 0.000). The rate of PCR positivity was lower in those working in the COVID-19 unit and using appropriate PPE compared to others. The PCR positivity rate (88.9%) in the security staff was significantly higher than that of the others. While none of those using PPE in social areas used by in-hospital healthcare personnel had PCR positivity, 23.4% (n = 84) of those who did not use PPE had a positive PCR test result.

While PCR positivity rate was only 11% in patients with a history of contact with COVID-19, 100% of those with a history of contact with a family member of COVID-19, 54.5% of those with a history of out-of-hospital social contact with COVID-19, and 21.6% of those with a history of social contact with in-hospital healthcare professionals had a positive PCR test. PCR results were found to be positive in 86.2% (n = 25) of those who did not use any PPE (Table 5).

Table 1. Protective equipment recommended being used for COVID-19 disease in terms of healthcare facility, staff and type of activity

Area	Target Staff	Type of Activity	Type of Personal protective equipment/procedure
Sickroom	Medical staff	Direct care of the patient	Medical (surgical) mask Apron Glove Visors/face shields
		Droplet / aerosol-forming procedures	N95 / FFP2 Mask Apron Glove Visors / face shields
	Cleaning staff	Entering the patient's room	Medical mask Apron Glove Visors/face shields (if there is a risk of organic material or chemical splash
All other areas where patient transfer takes place (such as clinics, corridors)		All activities that will provide contact with the patient, including healthcare professionals	Medical mask
Triage	Medical staff	Preliminary assessment without direct contact with the patient	At least 1 meter of distance should be kept. Medical mask Visors / face shields
	Patients with/without respiratory symptoms	In every case	At least 1 meter of distance should be kept. The patient should wear a medical mask.
	Administrative staff such as security/secretary etc.	In every case	At least 1 meter of distance should be kept. Medical mask
Lab	Lab technician	Studying respiratory samples	N95 / FFP2 mask Apron Glove Visors/face shields
Office area	All staff, including medical staff	All administrative tasks that do not require contact with patients	Keeping social distance Medical mask if not

Table 2. Assessment of the Healthcare Professional's contact status with the COVID-19 patient

	Healthcare Professional's Use of Personal Protective Equipment (PPE)	Contact Risk
Intense contact with COVID-19 patient wearing a medical (surgical) mask	Not using a medical mask or N95, or used a medical mask in case of N95 indication	Moderate
	Not using eye protection	Low
	Not using gloves and aprons	Low
	Using PPE appropriately	No risk evaluated
Intense contact with COVID-19 patients without a medical mask	Not using a medical mask or N95	High
	Using a medical mask in case of N95 indication	Moderate
	Not using eye protection	Moderate
	Not using gloves and aprons	Low
	Using PPE appropriately	No risk evaluated

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Table 3. The work type of healthcare professionals, their working status in COVID-19 units, PPE use, contact history of COVID-19 infection and distribution of contact risk

		n	%
Duty	Nurse	197	5.,4
	Doctor	76	20.6
	Cleaning staff	38	10.3
	Lab and X-ray Technician	25	6.8
	Office worker	11	3
	Security guard	9	2.4
	Administrative Services	3	0.8
	Pharmacist	2	0.5
	Other	8	2.2
Working status in COVID-19 units	Yes	202	54.7
	No	167	45.3
PPE use during risky contact in COVID-19 combat units	N95 / FFP3 + Apron + Goggles / Visor + Gloves	118	32
	Surgical Mask	105	28.5
	Surgical Mask + Apron + Goggles / Visor + Gloves	99	26.8
	No equipment	29	7.9
	N95 / FFP3 + Overalls + Apron + Goggles / Visor + Gloves	18	4.9
PPE Use in Hospital Social Areas	No	354	95.9
	Yes	15	4.1
Contact history of COVID-19 infection	In-Hospital Social Contact	171	46.3
	Patient Contact	146	39.6
	Healthcare Professional Contact	26	7
	Out-of-Hospital Social Contact	22	6
	Contact with a Family Member with COVID-19	4	1.1
Contact Risk	High	331	89.7
	Low	34	9.2
	Moderate	1	0.3
	No risk evaluated	3	0.8
	Total	369	100

Table 4. PCR and Thorax CT examination results and outcomes of the cases

		Frequency	Percent (%)
PCR	Negative	286	77.5
	Positive	83	22.5
CT findings	Negative	329	89.2
	Typical	21	5.7
	Atypical	19	5.1
Outcome	Continuing to work	260	70.5
	Isolation at home	96	26
	Hospitalization at service	12	3.3
	Hospitalization in the intensive care	1	0.3
	Total	369	100

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Table 5. Comparison of PCR results of the cases with the working status in COVID-19 units, use of PPE in COVID-19 suspected areas and in-hospital social areas, contact history and PPE use

		PCR		Chi-Square Analysis
		Negative n (%)	Positive n (%)	
The working status in COVID-19 units	No	116 (69.50%)	51 (30.50%)	X^2=11,327
	Yes	170 (84.20%)	32 (15.80%)	p=0,001
The use of PPE in COVID-19 suspected areas	No	1 (33.30%)	2 (66.70%)	X^2=15,839
	Yes	169 (84.90%)	30 (15.10%)	p=0,000
	Not working in COVID-19 units	116 (69.50%)	51 (30.50%)	
The use of PPE in in-hospital social areas	No	271 (76.60%)	83 (23.40%)	X^2=4,538,
	Yes	15 (100.00%)	0 (0.00%)	p=0,028
Duty	Nurse	160 (81.20%)	37 (18.80%)	X^2=33,381, p=0,000
	Doctor	56 (73.70%)	20 (26.30%)	
	Cleaning staff	26 (68.40%)	12 (31.60%)	
	Lab and X-ray Technician	23 (92.00%)	2 (8.00%)	
	Office worker	10 (90.90%)	1 (9.10%)	
	Security guard	1 (11.10%)	8 (88.90%)	
	Administrative Services	3 (100.00%)	0 (0.00%)	
	Pharmacist	2 (100.00%)	0 (0.00%)	
	Other	5 (62.50%)	3 (37.50%)	
Contact history	In-Hospital Social Contact	146 (78.40%)	51 (21.60%)	X^2=52,62, p=0,000
	Patient Contact	130 (89.00%)	16 (11.00%)	
	Out-of-Hospital Social Contact	10 (45.50%)	12 (54.50%)	
	Contact with a Family Member with COVID-19	0 (0.00%)	4 (100.00%)	
Type of PPE	N95 / FFP3 + Apron + Goggles / Visor + Gloves	107 (90.70%)	11 (9.30%)	X^2=83,03, p=0,000
	Surgical Mask	84 (80.00%)	21 (20.00%)	
	Surgical Mask + Apron + Goggles / Visor + Gloves	80 (80.80%)	19 (19.20%)	
	No PPE was used	4 (13.80%)	25 (86.20%)	
	N95 / FFP3 + Overalls + Apron + Goggles / Visor + Gloves	11 (61.10%)	7 (38.90%)	
Total		286 (77.50%)	83 (22.50%)	

DISCUSSION

Struggling at the forefront of the COVID-19 pandemic by providing treatment services to COVID-19 positive patients, healthcare professionals are at serious risk in terms of COVID-19 infection transmission. The importance of PPE use has been gaining importance in cases of confirmed or probable COVID-19 disease as well as in-hospital and daily life social contact areas.

A limited number of publications have reported that healthcare professionals are infected both in the workplace and in the community, mostly through infected family members. Healthcare professionals have been reported to be contaminated due to late COVID-19 diagnosis of patients, working in a high-risk department, longer working hours, inadequate hygiene, lack of training on infection prevention and control measures for respiratory pathogens, including COVID-19 virus, prolonged viral exposure in areas where a large number of COVID-19 patients are cared for, and incomplete or improper use of PPE (**2, 6, 8**)

During the study period, a total of 369 healthcare professionals who were evaluated in the Emergency Department of our hospital with COVID-19 symptoms or in the Employee Health Polyclinic due to high risk contact with COVID-19 positive patients, considering as possible COVID-19 cases were included in the study. 65.3% of the healthcare professionals in our study were females. When the distribution according to their occupation was examined, 53.4% of the cases were nurses, 20.6% were doctors and 10.3% were cleaning personnel. Similarly, in a study examining 43 health professionals, it was reported that the rate of females (84%) was higher than that of males and 51% of the nursing staff were affected by the infection (**9**). Similarly, in the CDC weekly reports, 73% of the healthcare professionals concerned were reported to be females. The fact

that the nurses are exposed to a higher risk of infection is that the majority of nurses are female, the number of nurses is higher than those with other titles, and they have proximity to patients during treatment administration.

In our study, the PCR test of 22.5% (n = 83) of the cases was found to be positive. Employee groups with the highest PCR positivity rate were security guards (88.9%), cleaning staff (31.6%), doctors (26.3%) and nurses (18.8%), respectively. The high rate of PCR test positivity in security guards and cleaning personnel may be due to the lack of training on the use of appropriate PPE and prevention measures from infection and the inefficient use of the required PPE.

When the COVID-19 contact risk groups were evaluated, it was determined that 89.7% of our healthcare professionals were in the high-risk contact group. Similarly, in another study, 121 patients, including 43 symptomatic healthcare professionals, were investigated and 3 COVID-19 positive healthcare professionals were identified as a result of multiple unprotected patient contact, especially during respiratory tract interventions, and it was emphasized that there should be no contact without PPE (**9**). At this stage, the use of appropriate PPE in patient management becomes very important. In our study, it was determined that the proper use of PPE at the point of contact with COVID-19 patients was associated with a negative PCR result with a rate of 84.9%.

COVID-19 can be transmitted with high potential even in asymptomatic patients, and this is enough to emphasize the problems that may be caused by the inappropriate use of PPEs. In some case reports published from Wuhan, it was reported that 14 healthcare professionals were infected with a patient even without a fever response, and significant transmission was caused by the patient who did not develop symptoms although substantial findings were detected in lung imaging. At this point, the exclusive use of PPE (N95, visor, protective apron) has been found to be very significant and effective, especially in protection from infection (**10-12**) . In our study, similar results were obtained. It was determined that the use of N95, protective apron, visor and gloves together provided protection at the rate of 90.7% in contact with COVID-19 patients. In addition to the effective use of PPE at patient contact points, the rapid and effective isolation of these patients may also minimize patient-induced contact with healthcare professionals, especially in emergency departments (**13**).

Although the importance of proper PPE use at the point of contact with COVID-19 patients in preventing disease transmission is considered at the forefront, it is not possible to completely explain the transmission among our healthcare professionals in this way. When the contact histories with COVID-19 infection are examined in our study; 46.3% of the cases had in-hospital social contact (PCR positivity rate 21.6%), and 39.6% of the cases had a history of contact with COVID-19 patients (PCR positivity rate 11%). 1796 (15%) of 12,022 healthcare professionals working in 3 hospitals in South Holland were screened and 96 (5%) of them were found to be COVID-19 positive. When the genome sequences from 50 healthcare professionals and 10 patients were examined, it was found that most sequences were in three and double groups showing the local circulation in the region. The patterns indicated were consistent with local empowerment in the community and multiple admissions to hospitals through community-based infections. At the onset of the COVID-19 outbreak in the Netherlands, it was reported that healthcare professionals were likely to be infected by the community rather than hospitals (**14**). This finding reveals the importance of PPE in contact areas with patients and attention to infection protection measures. In addition, it is crucial for healthcare professionals to keep the necessary social distance, wear masks and take necessary protective measures, both inside and outside the hospital.

In some reports regarding the inflectional status of the healthcare professionals, it was emphasized that 90% of the cases were followed by home isolation, while 2-5% were taken to intensive care support and 0.3-0.6% resulted in death (**5**). Similarly, in our hospital, 96.5% of the professionals were isolated at home or continued to work, while the need for intensive care was found to be 0.3%. No death cases were reported among healthcare professionals in our hospital. Early diagnosis and isolation of patients and early screening of healthcare professionals may have led to this result. Achieving survival with appropriate treatment, none of our healthcare professionals died due to COVID-19, even if some needed intensive care.

CONCLUSIONS

Healthcare facilities should follow CDC recommendations, country and local infection control and PPE procedures for the protection of healthcare professionals who contact with potential or confirmed COVID-19 patients. Early diagnosis of patients with possible COVID-19 infection and taking emergency isolation measures can reduce high-risk contacts of healthcare professionals. The level of knowledge of healthcare professionals should be increased in terms of the implementation of social isolation rules in in-hospital social areas as well as contact and treatment points with COVID-19 patients. Thus, the risky contact of healthcare professionals working at the forefront of combating the pandemic can be reduced.

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Effect of Sirolimus on Intra-Abdominal adhesion development in a rat model

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ABSTRACT

Objective: Postoperative intraabdominal adhesions still cause significant morbidity in surgical patients. This study aims to evaluate the effects of an immunosuppressor known as Sirolimus and an antiadhesive membrane which is formed with sodium hyaluronate carboxymethylcellulose-based bioresorbable membrane (Seprafilm™) to the intraabdominal adhesion formation in a rat model.

Materials and Methods: This experimental study was performed at an experimental research center, Yeditepe University Faculty of Medicine, Istanbul. Spraque-Dawley Rats, at a weight of about 250±20 gr, were used. Group 1 (n=8): Abdomen was closed after applying cecal abrasion (control group), group 2 (n=8): 10 x 30 mm Seprafilm™ was applied under the abdominal wall after cecal abrasion (Seprafilm™ group). Group 3 (n =8): Sirolimus (0,5 mg/kg) was applied (Sirolimus group). Adhesions quantitatively evaluated by a blinded assessor according to the classification of Nair and his colleagues.

Results: Statistically significant difference in terms of adhesion severity scores according to the Nair classification was found between the Sirolimus and the control group (p=0,03). Whereas, no statistically significant difference was found between the Seprafilm™ and the control group (p=0,17). Similarly, no statistically significant difference was found between Seprafilm™ and sirolimus group (p=0,64).

Conclusion: Although there was no statistically significant difference between intraperitoneal application of Sirolimus and Seprafilm™ group (p = 0.57), a statistically significant difference was found when each group compared with the control group (p=0,03). Combined anti-adhesive effect of Sirolimus and Seprafilm™ can be evaluated in future studies.

Keywords: Abdominal Adhesion, Experimental study, Sirolimus, Seprafilm

INTRODUCTION

Together with improved anesthesia and surgical techniques, the frequency of abdominal operations have kept on increasing nowadays, and due to this reason increase in postoperative intraabdominal adhesions have also been observed. The main surgical problems caused by adhesions are intestinal and enterocutaneous fistula formations, difficulty in relaparotomy procedures, and infertility in women. An agent having ideal characteristics that completely prevents adhesions could not be discovered yet, but this subject is one of the current research subjects. Following abdominal operations, the frequency of intraabdominal adhesions has been reported in varying rates between 67% to 93% (1). In a study, it has been reported that 5,5% of all of the hospital applications that have been made adhesion (2). The most severe complication of intraabdominal adhesions are intestinal obstructions. This situation is observed in 1-3% of the patients that apply to the general surgical clinics (3, 4). In addition to the medical problems that are caused by adhesion, its cost also leads to severe problems. More than 300,000 procedures are carried out every year for adhesiolysis in the United States of America (USA), and 1.3billion $ are spent annually for direct patient care related to said procedures. In England, the annual medical expenses caused due to adhesive small intestine obstructions add up to 12 million £ (5, 6).

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Several studies have been carried out regarding this first step of adhesion development until today, and although favourable results have been obtained, many results also had unwanted effects. As fibroblasts form the dominant cell type in the medium, in the latent period following the early inflammation phase, the usage of agents that may prevent the migration or activity of these cells has broadened up the horizon in preventing intraabdominal adhesions (**6**).

In this study, we aim to evaluate the effects of Sirolimus and sodium hyaluronate carboxymethylcellulose-based bioresorbable membrane (Seprafilm™) to the intraabdominal adhesion formation in a rat model.

MATERIAL and METHODS

This empirical study was accepted at the meeting dated 02.05.2011 of Yeditepe University Laboratory Animals Ethic's Committee and received confirmation with the decision number 187 of the Laboratory Animals Ethic's Committee. This empirical study has been carried out in the Emrpical Research Center of the Medical Faculty at Yeditepe University (YÜDETAM). Spraque-Dawley Rats with weights between 250±20 gr have been used as laboratory animals, which were bred in YÜDETAM and were fed with standard rat feed and water ad libitum. All of the animals were not fed food or water for 12 hours before a surgical operation. Three groups formed Group 1 (n=8): Control group, Group 2(n=8): Group treated with SeprafilmTM following cecal abrasion, Group 3(n=8): Group treated with Sirolimus following Cecal abrasion.

Operation Technique

The operations were carried out under semi-sterile conditions. Anaesthesia was established by intramuscu8lar injection of 50 mg/kg Ketamine hydrochloride (Ketalar, Pfizer İlaçları Lmt. Company, Istanbul, Turkey) and 4 mg/kg xylazine (Rompun, Bayer Türk Kimya San. Ltd. Company Istanbul, Turkey). During the trial, spontaneous respiration of the rats was enabled. A table lamp was used in order to maintain the body temperatures of the rats at 37˚C. All of the animals were shaved and cleaned and wiped with povidone-iodine. Laparotomy was carried out with a 25mm midline incision. The subjects were randomized to 3 different groups according to a random number table after abrasion was established in the first operation.

The aim of this operation was to form adhesion at a broad spectrum. A 20mm midline incision was made to the abdomen (**Figure 1**). The Cecum was found and taken out from the abdomen. The Cecum and the small intestines were carefully placed on wet gas, and some areas were abraded with a toothbrush. While this procedure was being carried out, only serosal injuries were created. The cecum front wall and different sections of the ileum intestine segment were abraded in all subjects using this method. After the Cecum and small intestine segments were placed in their first places, the abdomen wall was sealed with 4/0 absorbable suture (Vicryl) and 3/0 silk with double layers. At this stage, the subjects were randomized into the three different groups mentioned above.

1- In group 1 (n= 8), cecal abrasion was applied, and the abdomen was sealed (control group).

2- In group 2 (n=8), Following cecal abrasion, SeprafilmTM was applied (SeprafilmTM group) comprising 10x30mm hyaluronidase and carboxymethyl cellulose beneath the abdomen wall.

3- In group 3 (n=8), following cecal abrasion Sirolimus (0,5 mg/kg) was applied (Sirolimus group).

None of the rats that were included in the three groups monitored during the postoperative phase were lost due to anaesthesia. All of the rats were sacrificed with a high dose of ether in compliance with the Helsinki agreement on the 14th day. Furthermore, following this, U incision was made on their abdomens, and the abdomen walls were retracted downwards in order to provide a maximum view. Afterward, through the classification defined by Nair et al., the adhesions were quantitatively evaluated (**Table 1**) (**7**). **Figure 2** and **3** show macroscopic grade of adhesions. The evaluation was carried out as double-blind in compliance with the classification provided to a blind examiner.

Histopathological Evaluation

Pathological pieces were fixed in cups containing 10% buffered formol. The pieces that were monitored with classic laboratory methods were embedded into paraffin blocks. They were stained with hematoxylin-eosin and were examined with light microscopy (**Figure 4 and 5**). The pathologist that carried out the examination did not know which group the pieces were taken from. Following the histopathologic evaluation, the pieces were subjected to microscopic classification defined by Zühlke (**8,9**) (**Table–2**).

Statistical Evaluation

Statistical Packages for Social Science (SPSS 15,0 for Windows Evaluation) program was used in order to evaluate data and to carry out comparisons between groups. A chi-square test was carried out for categorical data analysis. Values less than 0,05 were accepted to be statistically significant p values.

RESULTS

When the group applied with Sirolimus was compared with the Control group, a statistically significant difference was found (p=0,03) in terms of adhesion severity scores, according to Nair (**Table 3**) classification. However, despite this, a statistically significant difference was not observed (p=0,17) between the control group and the group treated with SeprafilmTM. Similarly, a statistically significant difference was not observed between the group treated with SeprafilmTM and the group treated with Sirolimus (p=0,64).

While statistically significant difference (p=0,03) was found when the group treated with Sirolimus was compared in terms of microscopic adhesion grading of the control group similar to macroscopic grading during the histopathologic evaluation, and when compared with the group treated with SeprafilmTM a statistically significant difference could not be found (p=0,09). At the same time, a statistically significant difference (p=0,57) could not be found between the group treated with SeprafilmTM and the group treated with Sirolimus.

The values obtained by using Zuhlke classification during the histopathologic evaluation were shown in **Table 4**.

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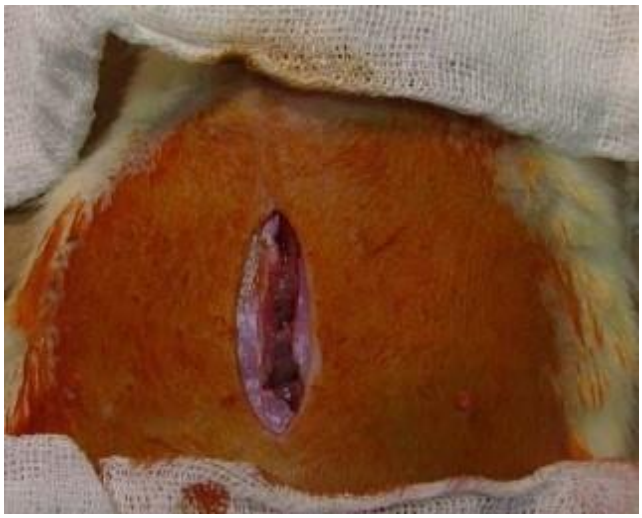

Figure 1: Abdominal Incision

Table 1: 'Nair' macroscopic adhesion classification

Grade 0: No ahdesion
Grade 1: A single adhesive band between the organs or between the organ and the abdomen wall
Grade 2: Two adhesive bands between the organs or between the organ and the abdomen wall
Grade 3: More than two adhesive bands between the organs or between the organ and the abdomen wall or intestinal adhesions without adhesion to the abdomen wall
Grade 4: The viscera being directly adhered to the abdomen wall

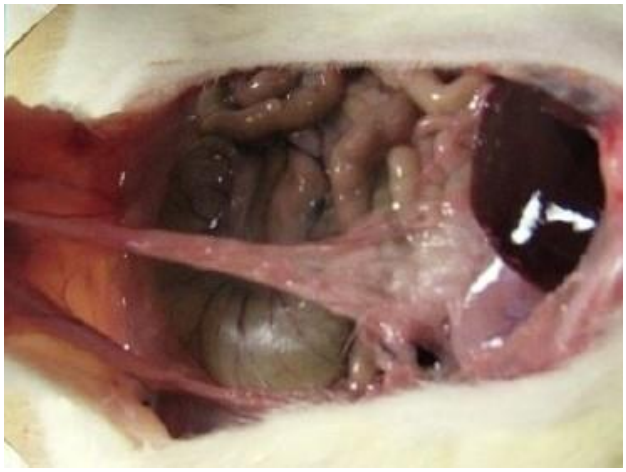

Figure 2: Macroscopic grade 1 adhesion

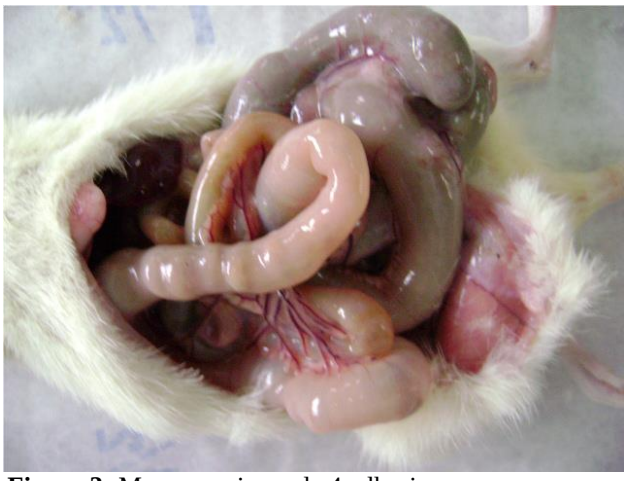

Figure 3: Macroscopic grade 4 adhesion

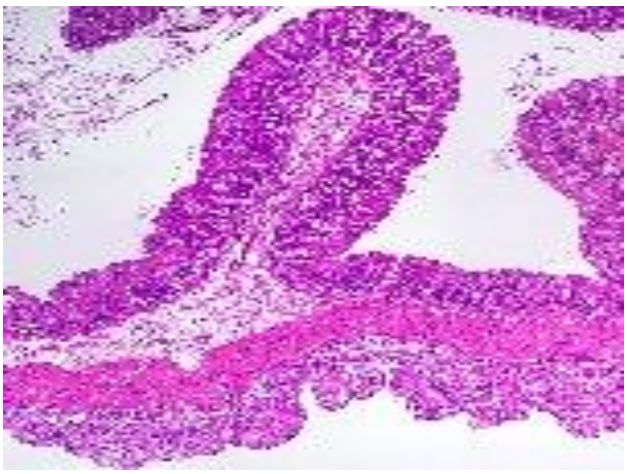

Figure 4: Microscopic image of inflammatory cell infiltration (Haematoxylin-eosin staining x100)

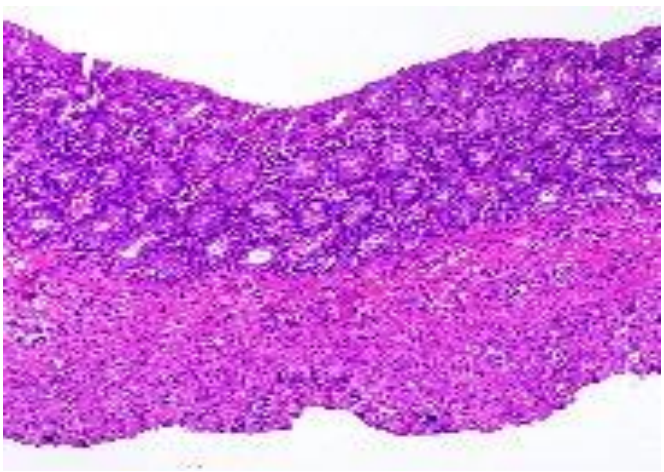

Figure 5: Microscopic view of Fibrosis (Haematoxylin-eosin staining, x100)

Table 2: 'Zühlke' microscopic adhesion classification (grading)

Grade 1: Weak connective tissue, abundant cell, old and new fibrin, thin reticular fibrils
Grade 2: Connective tissue with cells and capillary vessels, rare collagen fibers
Grade 3: Thicker connective tissue, rare cells, and more vessels, rare elastic, and straight muscle fibers
Grade 4: Old thick granulation tissue, poor in terms of cells, difficult separation of serosal layers.

Table 3: Adhesion severity scores according to Nair classification

Adhesion Score	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)
0	0	2	3
1	1	3	4
2	2	2	1
3	2	1	0
4	3	0	0

Table 4: Microscopic adhesion grading according to groups

Subject	Control	Seprafilm™	Sirolimus
1	3	2	1
2	4	3	1
3	3	1	2
4	2	2	2
5	2	2	1
6	2	1	2
7	4	1	2
8	4	2	2

DISCUSSION

Postoperative intraabdominal adhesion is one of the basic problems that cause severe morbidities such as pelvic pains, infertility, intestinal blockage, and ureter obstructions (**10, 11**). Besides the additional morbidity, it poses for patients, it is also a financial burden for countries' economies. A method that prevents abdominal adhesion prevents repeating operations, and the morbidity and financial burden said operations bring about (**8**). There are some studies, in order to prevent adhesions that have been carried out (**5,12**). Although laparoscopic techniques and minimally invasive surgery have been adopted in order to reduce the trauma that may occur during a surgical intervention, surgical technique on its own is not sufficient to reduce postoperative adhesions and complications related to adhesions (**6**). As the improvement of surgical procedure had its limitations, physical barriers, and the usage of pharmacologic agents in order to prevent adhesion formation have come into prominence. Large and small peritoneal defects heal at the same time, and mesothelial healing is completed within seven days (**9**). In contemporary approaches in order to prevent adhesions, peritoneal damages must be reduced during operation (minimal, invasive, surgical), the inflammatory response must be reduced, coagulation inhibition must be provided, fibrinolysis must be stimulated, and adhesion surfaces must be separated (**13**). The treatment strategies in the future in order to prevent adhesion; must aim to control cellular mediators in the peritoneal fluid at the beginning of the adhesion formation process. Among these mediators are IL-1a, TGF-a, EGF, TGF-b, IL–6 ve TNF-a. It is thought that IL-10 prevents adhesion (**14–17**). Moreover, the similarity of cytokine production between rats and humans in response to injuries to the peritoneum is emphasized (**18**).

The benefits of physical membrane barriers in preventing adhesions following surgical operations have been proved in several empirical studies (**19, 20**). Bioresorbable membrane (SeprafilmTM) comprising hyaluronidase and carboxymethyl cellulose is one of the substances which has the most significant efficiency. In the 1990s, following FDA approval, it has been used frequently in the USA. This material, which comprises hyaluronate and carboxymethyl cellulose, has a film-like structure, and its efficiency has been proved in many experimental studies (**21**). Although it is widespread for physical barriers to have positive effects to be used, it is difficult for adhesion barriers to be applied directly to the damaged surface. Physical barriers that are used, particularly during laparoscopic surgery, are limited (**22**).

Moreover, although bioresorbable membrane (SeprafilmTM) comprising hyaluronidase and carboxymethyl cellulose are not deemed to cause high financial burdens in developed countries and are evaluated to be cost-effective, it is not valid in most of the countries. It is also challenging to apply besides the fact that it is expensive.

The efficiency of Rapamycin has been connected primarily to the protection of cytokines during the inflammation phase, which is the first step in adhesion pathology and to the prevention of fibroblastic activity, which is the second step in the process following the inflammation phase. It is known that TGF-β increases adhesion formation significantly and that it causes surgical complications due to intensive adhesions has been shown that Rapamycin stops neovascularization by suppressing proinflammatory cytokines (**23, 24**).

The results of this study show that intraperitoneal application of Rapamycin, with its antiproliferative efficiency against T lymphocytes and selectively fibroblasts, reduces adhesion development significantly relative to the control group. No difference could be found between the control group and the group treated with SeprafilmTM. Although a statistically significant difference was not observed between the SeprafilmTM and Sirolimus group macroscopically and microscopically, it has been found to be meaningful for a statistically significant difference to be observed between the control group and the Sirolimus group. Under the scope of these results, and by keeping in mind that microscopic evaluation is a more objective evaluation in comparison to macroscopic evaluation, it can be said that the intraperitoneal usage of Rapamycin gave results that were superior to many agents that have been used until today in order to prevent adhesion formation.

CONCLUSIONS

Nowadays, the adhesion preventive effect of Sirolimus, which is frequently used in renal transplant patients, should be researched into as much as SeprafilmTM, and its usage as a combination with SeprafilmTM or on its own should be taken into consideration.

Author Contributions: SB, KE, KB, ME: Literature Search, Study design, Surgical interventions and Data collection, Biochemical and Statistical Analyzes, **KE:** Article writing and revisions. Final approval for publication.

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Clinical and histopathological analysis of metastatic brain tumours: A single-centre experience

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ABSTRACT

Objective: The aim of this study is to determine the demographic and clinical findings of cases which have been operated for a brain mass and have metastasis, to analyse the histopathological findings, to draw attention to the molecular tests that are effective in the treatment of the primary tumour, and to compare our results with the literature data.

Material and Methods: One hundred seventy cases diagnosed with brain metastasis tumour between January 2012-2021 were analysed retrospectively. The clinical findings and demographic information of the cases were recorded from the hospital information system. The diagnoses of the patients diagnosed with metastasis, the analysis of the cases with or without a primary tumour at the time of diagnosis, and the immunohistochemical staining applied to detect the primary metastasis were recorded.

Results: Sixty-seven of the cases were female, and one hundred three were male. The youngest case was 14, and the oldest case was 90 years old (Mean 55.6 ± 14). While the clinical findings in 35 of the cases were solely headache, 41 patients also had at least one of the symptoms such as dizziness, seizure, weakness, and ataxia in addition to headache. The primary was unknown at the time of diagnosis of brain metastasis in 63 of the cases. There was a single focus in 107 cases, and multiple metastasis focus in 63 patients. Among all cases, lung (84), breast (24) colorectal (15), kidney (9) metastases were the most common. Primary focus could not be detected in 2 of the cases (neuroendocrine carcinoma and adenocarcinoma) despite all imaging techniques as well as immunohistochemical findings.

Conclusion: The possibility of metastasis is also present in cases with a single lesion and whose primary diagnosis is unknown, and histomorphological analysis become inevitable due to the increase in molecular examinations and the development of patient-specific treatment protocols. Besides, it should not be forgotten that the most common tumour-causing brain metastasis -whether or not the primary is known- is the lung. Kidney tumours may also present with metastasis without manifesting themselves.

Keywords: metastasis, brain, pathology, immunohistochemistry

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INTRODUCTION

Brain metastasis is ten times more common in adults than primary tumors of the brain. Frontal lobe and cerebellum are the regions where metastases are detected most frequently. Brain metastasis can be seen in approximately 10-30% of cases with a diagnosis of primary tumor. In cases with brain metastasis, the lifetime suddenly becomes shorter and may be shorter than 2 months on average (**1**). The prognosis of cases with brain metastasis varies according to the location of the primary tumour. Lung cancer can metastasise within an average of 4.5 months after diagnosis, and the breast within 41 months (**2-4**). Tumour species that metastasise to the brain are lung, breast, melanoma, and colorectal tumors in order of frequency (**5, 6**). In cases with a primary diagnosis in any organ, metastasis is considered in the presence of a single or multiple lesions in the brain. However, in cases with no primary tumour diagnosis or with single metastasis, high-grade central nervous system tumours are also included in the differential diagnosis. In the treatment of metastatic brain tumours, chemotherapy, fractionated radiotherapy or whole-brain radiotherapy (WBRT) are among the methods used along with surgery (**6**).

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When metastatic foci is single, they can be removed by surgery or stereotactic surgery; however, surgery cannot be performed since multiple metastases can occur in approximately 80% of the cases (**6, 7**). Increasing molecular studies and initiation of target therapies are significant for some primary tumors and its subtypes such as small cell lung carcinomas, melanoma, breast, and kidney cancers (**2**). Most of the brain metastases are resistant to chemotherapeutics; nevertheless, the systemic effects of the drugs used are utilised. Considering that the lifetime of patients with brain metastasis will be short, diagnosis and determination of the primary organ play a vital role in patient management and treatment in metastasis surgery.

MATERIAL and METHODS

The study included patients who had opere at Bezmialem Vakıf University Faculty of Medicine between January 2012-2021, and who had brain and medulla spinalis metastasis. The clinical findings and demographic information of the cases were recorded from the hospital information system. The diagnoses of the patients diagnosed with metastasis, the analysis of the cases with or without a primary at the time of diagnosis, and the immunohistochemical staining applied to detect the primary metastasis were recorded. The obtained findings were compared with the literature findings.

Statistical Analysis: Data were analysed with IBM SPSS Statistics 22.0 package program. Median, mean standard deviation values, frequency, and percentage values were given as complementary statistics. The study was approved by the Ethics Committee of Bezmialem Vakif University with the approval number 2021/125.

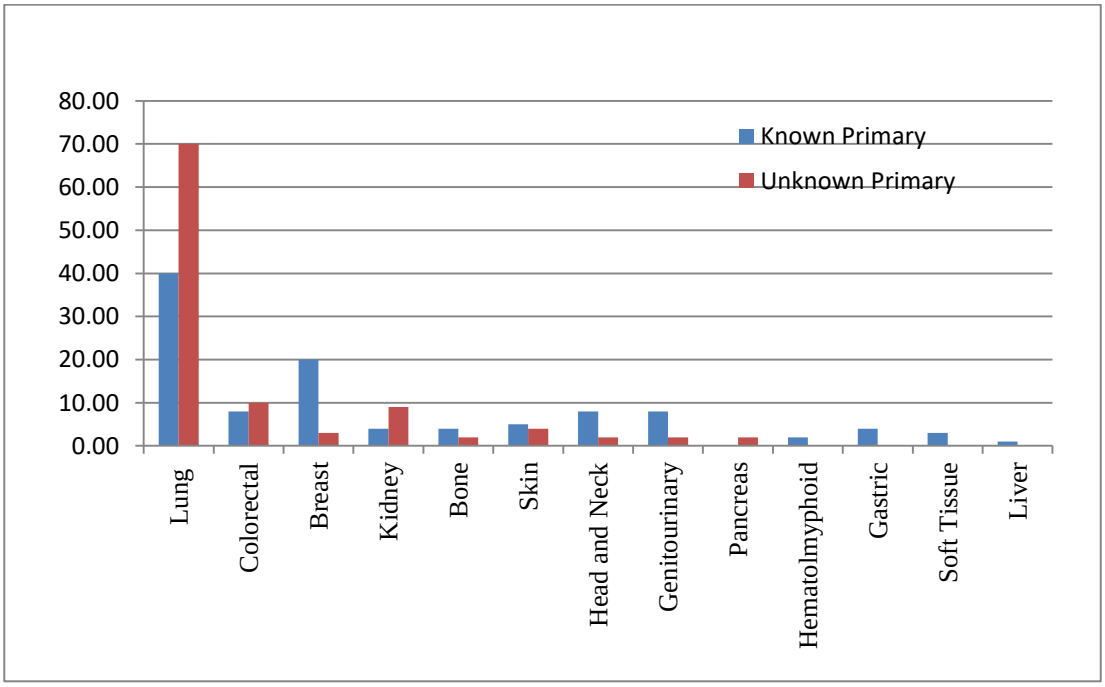
RESULTS

The 67 of 170 cases included in the study were females, and 103 were males. The youngest case was 14, and the oldest patient was 90 years old (Mean 55.6 ± 14).

Whereas the most common location was the cerebellum(45), followed by the frontal (36), medulla spinalis (20), parietal (16), temporal (16), occipital (15) lobes. Metastasis was present in two different lobes in 18 cases, in the sella in 1 case, and in the intraventricular region in 12 patients.

While the clinical findings in 35 of the cases were solely headache, 41 patients also had one of the symptoms such as dizziness, seizure, weakness, and ataxia in addition to headache. Furthermore, weakness, and numbness in the extremities, speech disorder and dysmnesia were other findings. Primary malignancy was not known at the time of diagnosis in 65 brain metastases. There was single focus in 107 cases, and multiple metastasis focus in 63 patients. The diagnosis was adenocarcinoma in 126 (74.1%) of the cases, squamous cell carcinoma in 17 (10%), 11 (6.5%) small cell neuroendocrine carcinoma, 7 (4.1%) cases malignant melanoma, 7(4.1%) cases sarcoma, 2 (1.2%) cases were lymphoma (**Figure 1**). Among all cases, lung (84), breast (24) colorectal (15), kidney (9) metastases were the most common. The primary focus could not be detected in 2 of the cases (neuroendocrine carcinoma and adenocarcinoma) despite all imaging techniques as well as immunohistochemical findings. The mean time elapsed between cases with a definite primary tumour and brain metastasis was 34.6 months, and the latest metastasis (38 years) was thyroid papillary carcinoma metastasis. Thirty-one of the cases were still alive, and 139 died.

When metastatic lesions are found, a graph of tumours with unknown primary and cases with known primary are given in the **Graph 1**. Except for two tumours where the primary focus could not be detected, considering the primary of 63 cases whose primary was unknown during metastasis, Lung was 44 (69.8%), Colon was 6 (9.5%), Kidney was 5 (7.9%), Breast was 2 (3.2%), Skin was 2 (3.2%), Bone was 1 (1.6%), Pancreas was 1 (1.6%, Prostate was 1 (1.6%), and Thyroid was 1 (1.6%).



Graph 1. Table comparing which organ/system tumors originate from primary and unknown primary tumors during the diagnosis of brain metastasis. Values are given as %.

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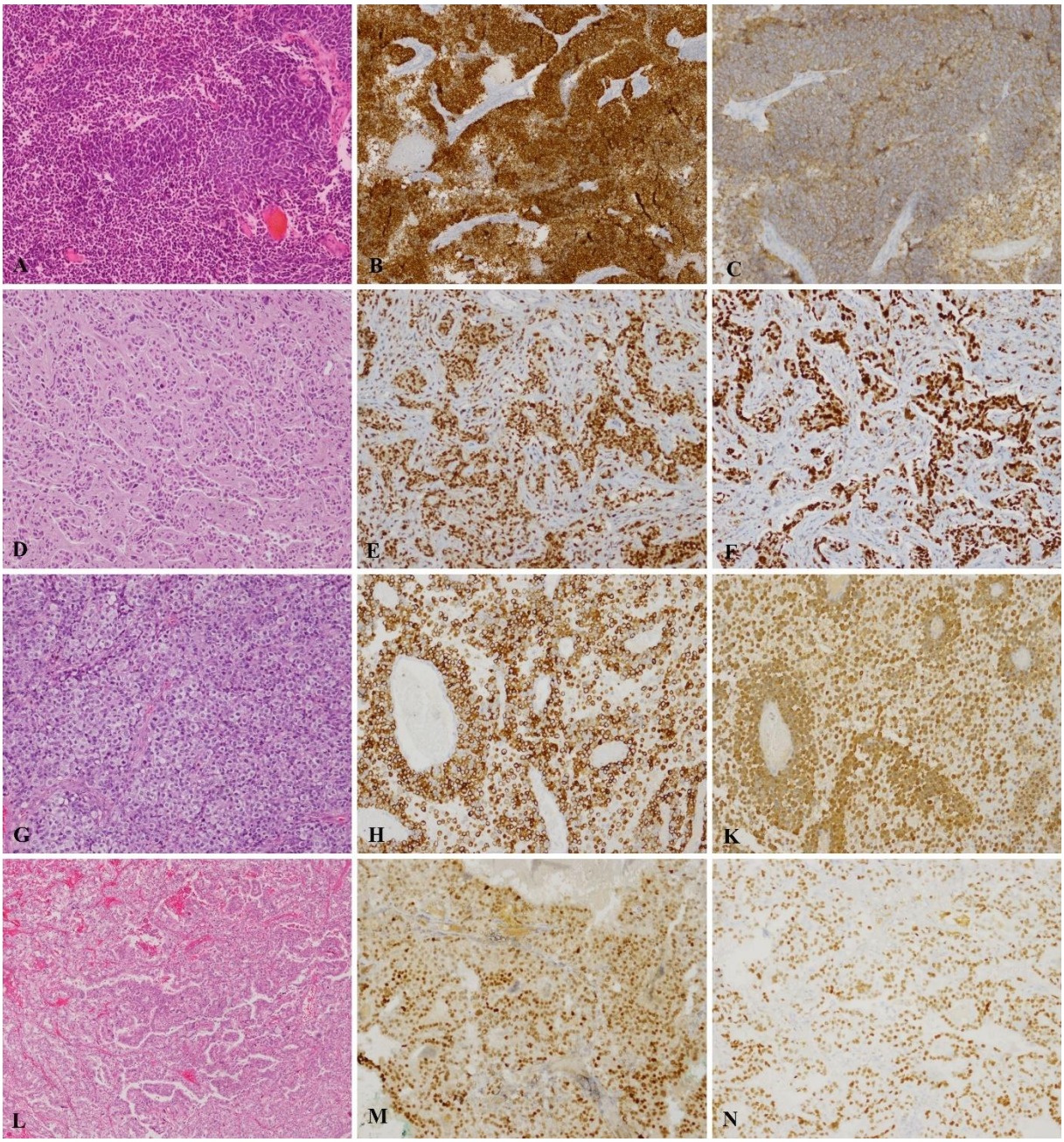

Figure 1. Small cell lung carcinoma (A, H&E), immunohistochemical TTF1 (B) and Synaptophysin staining (C), Breast carcinoma metastasis (D, H&E), immunohistochemical GATA (E) and Estrogen staining (F), Malignant melanoma metastasis (G, H&E) , immunohistochemical Melan A (H) and S100 staining (K), Thyroid papillary carcinoma metastasis (L, H&E), immunohistochemical PAX8 (M) and TTF1 staining (N). Original magnification x100)

DISCUSSION

Metastases are the most common cause of brain tumors in adults and are 10 times more common than primary brain tumors (5). This rate is increasing more with the development of imaging techniques. The most common areas where metastases are seen are the brain, cerebellum, and brain stem, as in our study, and rarely in the choroid plexus and suprasellar localisations. 12 metastases were found in the choroid plexus and 1 in the suprasellar region in our study. Hematogenous spread through arteries is often expected in brain metastases.

Metastases are often occur in the area between the middle cerebral artery and the posterior cerebral artery. In our study, metastases were most frequently seen in the frontal lobe between the middle cerebral artery and anterior cerebral artery, and then in the parietal lobe.

However, the retrograde perineural spread can also be seen, particularly in head and neck tumours (8). The primary of 8 of our cases are head and neck tumours.

In the literature, primary tumour focus includes lung, breast, melanoma, and colorectal tumours in the top four. In our study, lung, breast, colorectal tumours, and kidney metastasis were found in the top four. Contrary to the literature, considering tumours with known and unknown primary during metastasis, in cases with known primary during metastasis, there are lung, breast, colon metastases, respectively; while it was observed that lung, colon, and kidney metastases were more common in cases of unknown primary. Although lung metastasis is in the first place in both groups, it has a rate of 40% in those with a known primary and around 70% in the group with an unknown primary. Among the immunohistochemical markers applied to detect the tumour in the primary unknown group, TTF1, CK7 for lung, CK20, SATB2, CDX2 for colon, RCC, PAX8 for kidney, S100, HMB45, and SOX10 for melanoma are the most widely used. The right panel should be used after the prediction for the primary in the company with morphological findings. Considering that almost 70% of tumours with unknown primary are lungs, we emphasise that it should not be forgotten that lung metastasis should be excluded, and kidney metastases take the third place among those with unknown primary tumours.

The presence of extracranial metastasis determines the patient's condition, the location, number, and diameter of the tumour, and the condition of the primary tumour (**9**). Along with the increase in systemic treatments, the improvement of imaging techniques, and the improvement of supportive therapies, progression-free survival has been observed recently (**10**). However, although the primary focus was detected and treated in some of the patients, there is a group with a short lifetime. This is due to the genetic heterogeneity in the primary tumour and the metastatic tumour (**11**). Particularly the mutations in non-small cell lung carcinoma (NSCLC) and melanoma, and the hormone receptor status in the breast affect the prognosis. Brain metastasis is observed in approximately half of the patients during the course of NSCL carcinoma (**12**). Epidermal growth factor mutation (EGFR), which is seen in 15% of NSCLDs, is particularly associated with adenocarcinoma histology, under 35 years of age, non-smoker, and Asian patients. The presence of an EGFR mutation affects the response to tyrosine kinase inhibitor therapy (**13**). Breast tumours are the other tumour that most frequently metastasises to the brain after NSCLC. In breast tumours, as well as TNM staging and tumour subtype, being younger than 40 years old, presence of lung metastasis and performance status also affect the prognosis. The basal-type brain metastasis development time is relatively short among tumour types, as in the Sperduto et al. study (**14**). Of our 24 breast tumours with brain metastasis, 8 had basal, 9 had luminal B, and 6 had HER2 type, the data of two cases could not be reached, and luminal A was not present. The time between primary tumour diagnosis and metastasis was the shortest in basal type. About half of melanomas, which comprise 10% of brain metastases, particularly in young patients, have BRAF mutation. The presence of BRAF mutation is significant for treatment. However, it is not effective in predicting the development of brain metastasis or increasing the risk (**15**).

CONCLUSIONS

In addition to histomorphological findings, an increase in the variety of molecular examinations and immunohistochemical stainings presents a valuable guide in the distinction of primary metastasis. It should not be forgotten that the most common tumour-causing brain metastasis-whether or not the primary is known- is the lung, and kidney tumours may also present with metastasis without manifesting themselves.

Author Contributions: GÇ, ZS, FG: Literature Search, Study design, Surgical interventions and Data collection, Biochemical and Statistical Analyzes, **GÇ:** Article writing and revisions. Final approval for publication.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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The relationship between occupational accidents and the safety climate of blue-collar workers in the metal industry

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ABSTRACT

Objective: This study aims to reveal the ability of a safety climate assessment to make predictions regarding occupational accidents that occur in a metal sector workplace.

Material and Methods: This cross-sectional study was conducted with metal sector workers. Two sub-dimensions, the security climate scale, and an 18-question form, were used for data collection. The Chi-square, 'Student's t-test, and logistic regression tests were used to determine the relationships with occupational accidents. A correlation analysis was applied between the total scale score and its sub-dimensions.

Results: The questionnaire was completed by 289 workers (90.1%). In their current workplace, 28.4% had at least one work accident. The total score of the occupational safety climate was 61.11±6.90, and each unit was observed to increase the occupational safety climate score provided there was a 4.6% (95% CI: 0.6–8.4%) decrease in occupational accident reporting. There is a 1.10 (95% CI: 1.04–1.17) fold rise in reported work injuries for every additional year the workers work in this workplace (p = 0.001). Compared to unmarried people, married people recorded 3.24 times (95% CI 1.02–10.35) more workplace injuries.

Conclusion: According to the data, employee safety monitoring mediates the relationship between a safe environment and occupational accidents.

Keywords: Occupational health; metal industry; safety climate; occupational accidents

INTRODUCTION

One thousand employees die every day due to workplace accidents and 2.3 million people per year due to unsafe workplace conditions (1). The economic burden caused by work-related diseases and deaths constitutes 4% of the gross domestic product (2). The 2016 cost of occupational injuries and occupational diseases in Turkey is estimated to be greater than 100 billion US $ (3). In 2016, the metal industry ranked fifth with 4.06% in terms of the activity groups with the highest number of deaths due to occupational injuries and diseases (4).

In Iran, an epidemiological study was investigating the rejection of preventive training for occupational accidents and the lack of widespread use of appropriate PPE in the metal sector, it pointed out the scarcity of occupational health and safety professionals as an element of safety culture (5). Occupational injuries in a metal factory in Ankara have been associated with the lack of vocational training and problems with the usage of personal protective equipment (PPE) (6). In addition, studies are suggesting that non-occupational factors and personal characteristics associated with occupational injuries should also be taken into account (7, 8).

There are hints of a complex, albeit negative, the relationship between the safety climate and occupational injuries (9–11). It has been determined that employees who perceive the workplace as safe have fewer occupational injuries (11–14). Safety climate is the perception of workers in the work environment towards job security (15).

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Cooper and Phillips stated that the development and testing of theoretical models examining the relationship between the safety climate and occupational injuries is one of the essential stages in the development of the work safety climate literature (**16**).

This study aims to reveal the ability of a safety climate assessment to predict occupational accidents for blue-collar workers in a workplace operating in the metal sector in Ankara.

MATERIAL and METHODS

There are 320 blue-collar employees in the workplace that has been operating in the metal sector for about 30 years in Ankara. The occupational health and safety service organisation is provided with an institutional infrastructure. This cross-sectional study aims to cover all blue-collar workers working in a workplace operating in the metal sector in Ankara and is not sampled.

Data collection process and tools

The participants were contacted by the workplace doctor, who is one of the researchers, through regular health checks between September and November 2019. Although the occupational accident experienced by the employees in this workplace are recorded, they were interviewed face to face in order to include any notifications that may not have been recorded. In addition, an 18-question questionnaire containing personal characteristics and working conditions was used.

The occupational safety perception was evaluated with the Safety Climate Scale consisting of 14 statements. The Turkish adaptation and validity of the scale developed by Choudhry, Fang and Lingard in 2009 were carried out by Türen et al. in 2014. Management's perspective and rules were examined with ten propositions, and colleagues and safety training with four propositions (**17**). Each statement was scored with a five-point Likert scale (1: strongly disagree, 5: strongly agree), and the total score was included in the analysis.

Statistical Analysis : SPSS (version 23.0) was used in the study's analysis. Descriptive data were analysed using frequency, mean, and median. The Chi-square test and Student's t-test were used to examine the relationships between work accident experiences and individual factors, demographic characteristics, working conditions, and the occupational safety climate. Logistic regression analysis was performed to determine the corrected relationships of all explanatory variables to the dependent variable. Correlation analysis was applied between the scale total score and its sub-dimensions. The suitability of the data for factor analysis was examined using the Kaiser Meyer Olkin (KMO) value. Exploratory factor analysis was used to determine the 'scale's success in measuring the predicted structure. In addition, the correlation between each item in the scale and the dimensions were examined. 'Cronbach's alpha coefficient was calculated for internal consistency. A possible 'Cronbach's alpha value above 0.7 was accepted as a good consistency criterion. The significance value of the analyses was accepted as $p<0.05$.

Ethical approval: Ethical approval of the study was given by the Medical Research Ethics Committee of the Ege University Faculty of Medicine (with decision number 19-8.IT/11, dated 21.08.2019). Permission was obtained from the workplace managers for the participation of the occupational physician. All participants were informed about the purpose of this study, the duration of the interview, and their right to decline or withdraw; then, verbal and written consent was obtained.

RESULTS

Two hundred eighty-nine (90.1%) of 320 employees invited to the study answered the questionnaire. Eighty-two of the workers included in the study (28.4%) declared that they had an occupational accident at the current workplace. Two hundred eighty-eight of the participants were male, average age 36.6±7.9, 84.8% were married, 88.6% have had a minimum of a high school education. Only 12.5% of participants had an income that was higher than their expenses, only 29 (10.0%) of the employees stated that they received training on the job. The average number of years of experience in the workplace where participants are currently working is 7.6±7.6 (**Table 1**).

Table 1: The distribution of the characteristics of the employees according to their responses

Features		n*	%**
Age (36,6±7,9)	≤40	209	76.8
	>40	63	23.2
Gender	Female	1	0.3
	Male	288	99.7
Marital status	Single	40	13.8
	Divorced	3	1.0
	Widow	1	0.3
	Married	245	84.8
Education	Primary school and below	10	3.4
	Secondary school	23	8.0
	High school	196	67.8
	University and above	60	20.8
Alcohol use	Yes	43	14.9
	No	177	61,2
Smoking	Yes	169	58.5
	No	120	41.5
Accident at the current workplace	Yes	82	28.4
	No	207	71.6
Income and expenditure perception	Income <Expense	68	23.5
	Income = Expense	183	63.3
	Income> Expense	36	12.5
Occupational educated	Yes	260	90.0
	No	29	10.0
Workplace experience (years) (7,6±7,6)	0-5	149	51.7
	6-10	76	26.4
	>11	63	21.9

*There are missing data for some variables. ** Percentage of columns

The total score of the participants for the occupational safety climate was 61.11±6.90, the dimension of the managers' commitment to the security issue was 43.94±5.20 and the dimension of the colleagues and safety training was 17.16±2.25, shown in **Table 2**.

A high positive correlation was found between the total score of the scale and the sub-dimensions of the scale (Pearson Correlation, 0.970 and 0.827, respectively, $p <0.005$). There is a high positive correlation between scale sub-dimensions (0.666, $p <0.005$). When the correlation of the items in the scale with their dimensions was examined, it was seen that each item showed a higher correlation with its own dimension.

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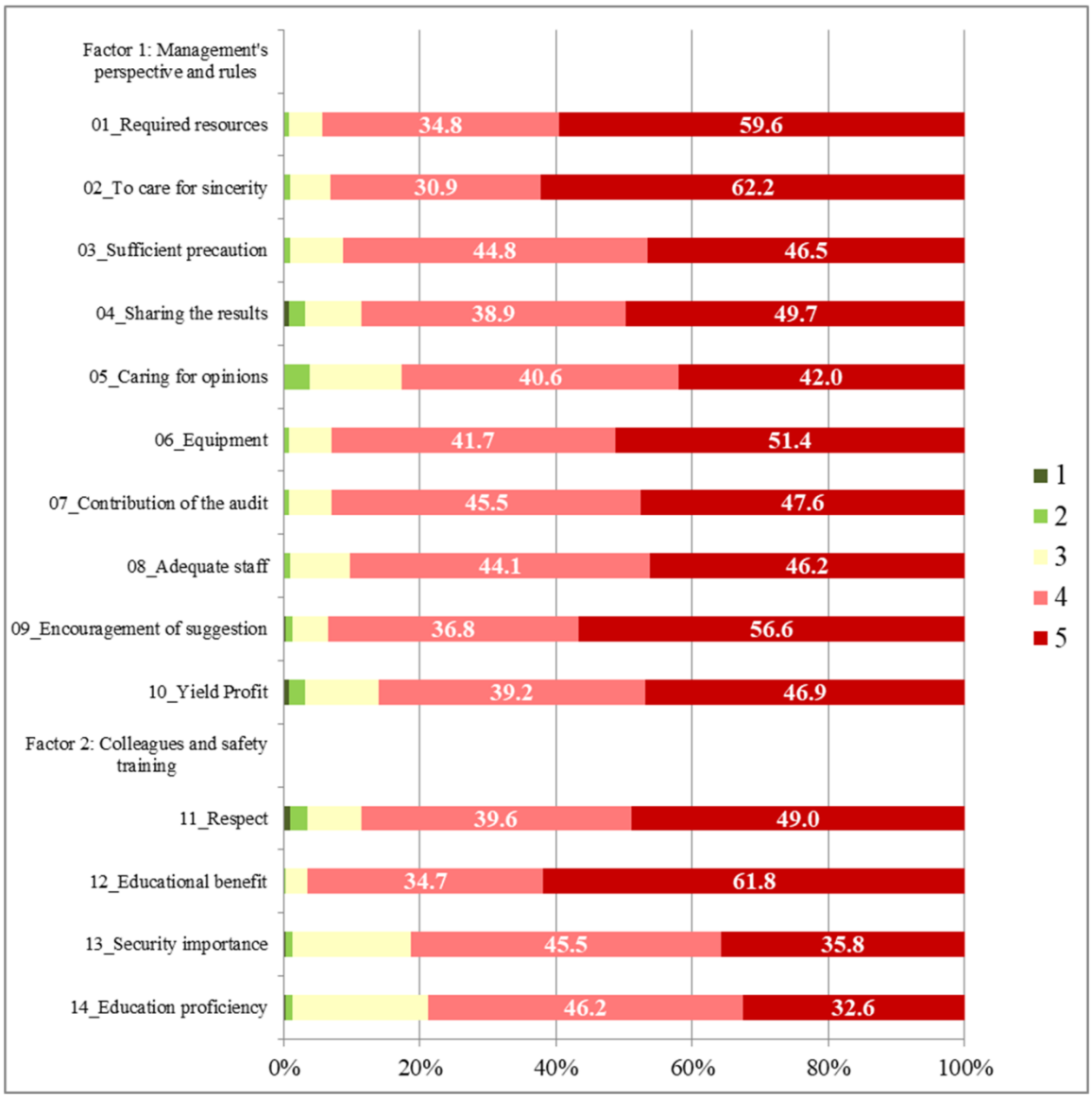
Table 2: Employees' Occupational Safety Climate Scale scores

	Mean	Sd	Median	Q1	Q3
Total Score	61.11	6.90	62	56	67
Factor 1: Management's perspective and rules	43.94	5.20	45	40	48
Factor 2: Colleagues and safety training	17.16	2.25	17	16	19



(1: strongly disagree, 5: strongly agree)

Figure 1: Percentage distribution of the responses given to the propositions

Table 3: Logistic regression assessment of factors associated with occupational injuries.

Features	Mean ± SD	Crude OR	95% CI		Adjusted OR*	95% CI	
Safety Climate	59.74±6.62	0.962	0.927	0.998	0.954	0.916	0.994
Age (years)	39.79±7.77	1.072	1.036	1.109	0.982	0.923	1.044
Workplace experience (years)	11.82±8.43	1.100	1.063	1.1439	1.103	1.039	1.170
Married	78 (31.8%)	4.671	1.614	13.513	3.244	1.017	10.348
Not married (ref)	4 (9.1%)		1.000			1.000	

KMO values of the data were 0.929 and 0.704 for the dimensions, respectively, while this value was 0.929 for the whole scale. The factor loads of the items varied between 0.536 and 0.819 for the sub-dimension of the managers' commitment to the security issue, while the only proposition for the coworkers and security dimension remained at 0.474, while the others varied between 0.709 and 0.879. The Cronbach's alpha values were 0.909 and 0.775 for the two factors, respectively. It was found to be 0.919 for the occupational safety climate scale. The percentage distribution of the responses of the employees to the items of the scale is shown in Figure 1. While the 12th item (96.3%) in the second sub-dimension (colleagues and safety training) had the highest positive (Strongly Agree + Agree) percentage of the items, the lowest percentage was the 14th item (78.8%) in the same dimension. For the first sub-dimension, the first item had the highest percentage (94.4%), while the fifth item had the lowest rate (82.6%)

Table 3 shows the factors associated with occupational injuries. According to the corrected logistic regression analysis, the score increase in the perception of occupational safety has a significant relationship with the decrease in work accident reporting. Each unit increase in the work safety culture score provides a 4.6% (95% CI: 0.6-8.4%) decrease in work accident reporting (p = 0.025). Each extra year that employees work in this workplace provides a 1.10 (95% CI: 1.04-1.17) fold increase in work accident reporting (p = 0.001). 3.24 times (95% CI 1.02-10.35) occupational accident reporting was realised in married people compared to unmarried ones. The relationship between age, which was determined in univariate analyses, and the state of having an occupational accident, lost its significance in the multivariate analyses (p> 00.5).

DISCUSSION

This study, which aims to reveal the relationship between work injuries and safety climate by making an assessment of the safety climate for blue-collar workers in a workplace operating in the metal sector in Ankara, has shown that; each point increase in the occupational safety climate provides a 5% reduction in occupational accident reporting. Increased safety measures contributed to the decrease in work accident indicators in the metal industry, as in all fields of work (**8, 14).** In workplaces where the occupational safety climate has increased, it is more common for employees to report risky situations before a work accident occurs (**18**). This provides opportunities for occupational health and safety professionals charged with managing risk, to provide safe work environments. For workplaces where a safe climate cannot be provided, the risk of occupational injuries becomes more pronounced. For example, in a cohort study conducted in Denmark, the OR 2.22 (95% CI 1.60–3.09) for reporting at least one accident in 2014 was found to be higher in those who reported three or more safety climate problems in 2012 than those who did not identify any safety climate problems in 2012 (**19**). Where the workplace safety climate is improved through cooperation between managers and employees, there is a positive effect on occupational safety performance (18).

As workplace safety has received increased attention (**8**) less-experienced workers are considered a higher risk for occupational accidents. However, in this study, there was a 1.1- fold increase, per year worked, in accident reporting for blue-collar workers. In the study carried out by Çınar et al. (2018) in the metal sector in Konya, it was reported that accident reporting of experienced employees was high, with more than half (56.37%) of those reports associated with employees with five or more 'years' experience (**20**). It is possible that as occupational accidents are unusual cases, those with more extended work experience will remember them more vividly.

In this study, the notification of an occupational accident in the metal sector was 3.2 times higher for married blue-collar workers than for those who were not married. This was found to be one of the variables associated with occupational accident reporting in Iran between 2008 and 2012, where married people reported more work accidents. The significance of this result was ascribed to married people working harder and taking dangerous duties because of increased responsibilities in the workplace (**21**).

In this study, 84.8% of the participants were married, with an average age of 36.6. Of this group, 88.6% had a minimum of a high school education, professional experience of 16.5 years, and current workplace experience of 7.6 years. In a similar study conducted by Gülhan et al. in a metal factory in Ankara in 2011, the average age was 35.4 ± 8.1, 88.0% of the group were married and had 15.5 ± 8.7 years of professional experience. However, the level of education shows a distinct difference (**6**). In a similar study conducted in India, the average age of island metal workers was 35.7 ± 7.4 years, 85% of the workers were married, 35% had a postgraduate education, and the average working time was 5.7 ± 1.9 years (**8**). However, as in the example for Addis Ababa, there were different profiles of participants conducting accident research in the metal sector, with less work experience and a lower educational profile (**22**).

There was a high positive correlation between the total score of the Occupational Safety Climate Scale, the sub-dimensions of the scale, and each item on the scale. This made it possible to discuss the relationship between the numbers of occupational accidents at work with the total score on the scale. However, the safety climate is a temporary phenomenon and subject to change. As a result, there are some variables that cannot be accommodated in this type of study.

CONCLUSIONS

According to this study, each point improvement in the occupational safety environment results in a 5% reduction in occupational injury reporting for blue-collar workers in a workplace working in the metal sector in Ankara. According to the data, employee safety monitoring mediates the relationship between the safety environment and occupational injury. In the metal sector, as in all fields of employment, increased safety measures lead to a decline in work injury indicators. These findings emphasise the importance of using organisational variables and employee characteristics to improve organisational safety performance.

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Effect of covid-19 pandemic on in-hospital mortality

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ABSTRACT

Objective: This study aimed to examine the effect of the pandemic on hospital mortality and patient admission in four months since March 2020 when the Ministry of Health announced the first confirmed COVID-19 case in Turkey and the first wave occurred.

Material-Method: This research is a single-centre, retrospective, cross-sectional descriptive study. It covers the periods between March 01 and Jun 30 of 2018, 2019, and 2020.

Results: Between 2018-2020, 897522, 972799, and 395438 patients were admitted to our Hospital, respectively. It was observed that the number of admissions decreased by 55-60% in 2020 compared to the previous years (p=0.001). Moreover, 205318 (22.9%) of the admissions in 2018, 229278 (23.6%) of the admissions in 2019, and 1127293 (32%) of the admissions in 2020 were emergency room (ER) admissions. Especially in 2020, there was a significant increase in the overall in-hospital (p=0.001) and ER (p=0.001 mortality rates compared to previous years. In-hospital mortality was found to be higher, especially in patients with suspected COVID-19 (p=0.001). It was found that the number of deaths due to respiratory causes was significantly increased in 2020 compared to the previous years (p=0.001).

Conclusion: The COVID-19 pandemic has led to significant changes in mortality rates and causes of mortality compared to previous years. Although the pandemic has affected all healthcare systems, ER and intensive care units (ICU) are seriously affected.

Keywords: COVID-19, mortality, emergency room

INTRODUCTION

Following its first description in Wuhan, China, Coronavirus disease 2019 (COVID-19) has become a severe health problem and has created a global crisis with its economic, sociological, and psychological aspects. The World Health Organization (WHO) declared this outbreak as "a public health emergency of international concern" on Jan 31, 2020 (1). The first case in our country was reported on Mar 11, 2020. As of June 13, 2021, WHO published 175.306.598 confirmed COVID-19 cases globally, and 3.792.777 patients died due to COVID-19 (2). In Turkey, as of June 13, 2021, a total of 5,330,447 COVID-19 cases and 48,721 deaths were reported (3).

Due to the immediate expanse of COVID-19 disease and the high hospitalization rate, it is essential to manage these patients well and organize hospital emergencies and departments to decrease their mortality rate. Analysis of hospital deaths is a crucial source of information for management (4). This research intended to analyze the impact of the pandemic on hospital mortality and patient admission in four months since March 2020 when the Ministry of Health announced the first confirmed COVID-19 case in Turkey and the first wave occurred.

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MATERIAL and METHODS

This research is a single-center, retrospective, cross-sectional descriptive study. The hospital mortality rates of the last three years (2018-2020) between Mar 01 and Jun 30 were scanned. March 01 to June 30 is the date range of the first pandemic wave in 2020.

The study included in-hospital deaths that occurred on the specified dates, patients brought by 112 ambulance teams while receiving Cardiopulmonary Resuscitation (CPR), and 396 patients brought by their relatives in cardiac arrest, received CPR, and died. After obtaining the study's ethical approval, the patients' files were reviewed through the hospital automation system, and the type of admission, admission complaint, diagnosis, and follow-up process were recorded in the study form by the researcher.

Patients without CPR indication brought to the emergency room (ER) as dead were not included in the study. Patients with thorax computed tomography (CT) findings of viral pneumonia but with negative PCR and patients with an International Classification of Diseases (ICD) code of Z03.0-9 were considered suspected COVID-19.

In contrast, patients with positive reverse transcription-polymerase chain reaction (PCR) or an ICD diagnosis code of U07.3 were considered COVID-19. Moreover, patients whose swab samples were collected and who underwent low-dose thorax CT and prepared for routine operation with negative findings were not considered suspected COVID-19.

The causes of death were divided into seven main classes: admission for the non-traumatic cardiac arrest of unknown cause, malignancy, respiratory causes, internal causes, surgical causes, neurological causes, and traumatic causes.

Admission for Non-traumatic Cardiac Arrest of Unknown Cause: Patients with no trauma in the etiology could not be diagnosed and brought while receiving CPR.

Malignancy: Patients with cancer and admitted for a reason other than respiratory tract pathology.

Respiratory Causes: Patients with ICD diagnosis codes of J96, J18, R06, U07.3.

Internal Causes: Patients with ICD diagnosis codes of N17, I10, K27, E14, D84, E87, I85, K92, T51, other toxicities, anemias, and extra-respiratory infections.

Surgical Causes: Patients with non-traumatic postoperative cardiac arrest, non-traumatic acute abdominal manifestations.

Neurological Causes: Patients with ICD diagnosis codes of I60-69, G40.

Traumatic Causes: Patients presented with a traffic accident, fall, hanging, firearm injury, sharp object injury.

IBM SPSS (Statistical Package for the Social Sciences) Statistics for Windows, Version 22.0 (IBM Corp. Armonk, NY, USA) was applied to investigate the collected data. Skewness and Kurtosis values were demanded to be in the range of -2/+2 for the data's normal distribution (5). The independent t-test was used for the comparison of customarily distributed measurable data. The Mann-Whitney U test was used for the comparison of non-normally distributed parameters. The chi-square test was applied for the association of qualitative data. A p-value of <0.05 (CI 95%) was considered significant for all analyses.

RESULTS

Between 2018-2020, 897522, 972799, and 395438 patients were admitted to our hospital, respectively. It was observed that the number of admissions decreased by 55-60% in 2020 compared to the previous years (χ^2=260884.187, p=0.001). Moreover, 205318 (22.9%) of the admissions in 2018, 229278 (23.6%) of the admissions in 2019, and 1127293 (32%) of the admissions in 2020 were ER admissions. Therefore, considering the rate of all hospital admissions, there was a significant increase in ER admissions, although there was a decrease in hospital admissions (χ^2=8159.556, p=0.001).

It was found that 99 people died in the hospital in 2018, 113 in 2019, and 184 people died in the hospital in 2020. Especially in 2020, there was a significant increase in the overall in-hospital (χ^2=479889.770, p=0.001) and ER (χ^2=42.426, p=0.001 mortality rates compared to previous years. There was an approximately four-fold increase in overall hospital mortality and a 2.5-fold increase in ER mortality. On the other hand, the ER share in in-hospital deaths in 2020 significantly decreased (χ^2=12.265), p=0.002).

Of 396 in-hospital deaths in 01 March-30 June in 2018, 2019, and 2020, 159 (40.2%) were female, and 237 (59.8%) were male. Considering the gender distribution of the deceased people by years, there was no significant difference (χ^2=0.414, p=0.813).

When the deceased people were analyzed by age, the mean age of the patients was 62.96 years, and the median age was 66.5, with the youngest age of 1 year and the oldest age of 98 years. Based on the age limit of 50, which is considered the age limit for treatment protocols according to the Health Ministry COVID-19 guideline for 01 March-30 June (6), there was no significant difference in overall hospital deaths by years. However, especially in 2020, there was a significant decrease in ER deaths under 50 years compared to previous years (χ^2=8.135, p=0.017). The patients' admission number by year and mortality rates are given in **Table 1**.

Of 395438 patient admissions in 01 March-30 June 2020, 127293 (32.2%) were ER admissions. In the same period, 29174 (96.5%) of the 30229 COVID-19 suspected patients' admission were ER admissions. Of the 184 patients who died in 2020, 92 (50%) had suspected COVID-19. Of the suspected COVID-19 deaths, 76 (69.1%) occurred in the COVID-19 ward and Intensive Care Unit (ICU), and 16 (29.9%) occurred in the ER.

The COVID-19 ward and ICU mortality rate of patients with suspected COVID-19 was statistically higher than the ER mortality rate (χ^2=37.332, p=0.001). Overall in-hospital mortality was higher, especially in patients with suspected COVID-19 (χ^2=283.673, p=0.001). There was no significant difference between patients' death at the ER, those with suspected COVID-19 and those without (χ^2=0.099, p=0.753). In addition, no suspected COVID-19 deaths under the age of 50 years occurred in the ER.

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The patients' demographic comparison is presented in **Table 2.** When the causes of death by years were analyzed under headings, it was found that the death number due to respiratory causes was significantly increased in 2020 compared to the previous years (χ^2=22.073, p=0.001).

Patients diagnosed with COVID-19 were primarily included in deaths due to respiratory causes since they presented with respiratory distress. In addition, there was a statistically notable reduction in deaths due to trauma (χ^2=8.168, p=0.017), malignancy (χ^2=6.907, p=0.032), and internal causes (χ^2=6.536, p=0.038). The mortality causes are shown in **Table 3**.

Table 1: Number of hospital admissions by years and mortality rates by age, gender, and unit

		2018		2019		2020		p-value
Total Number of Admissions		897522		972799		395438		p=0.001
Total ER Admissions		205318	22.9%	229278	23.60%	127293	32.2%	p=0.001
Total Hospital Mortality		99	0.01%	113	0.01%	184	0.05%	p=0.001
Total ER Mortality		43	0.02%	53	0.02%	74	0.06%	p=0.001
Hospital Mortality by Gender	**Female**	42	42.4%	46	41%	71	38.6%	p=0.812
	Male	57	57.6%	67	59%	113	61.4%	
ER Mortality by Gender	**Female**	16	37.2%	17	32%	29	39%	p=0.709
	Male	27	62.8%	36	68%	45	61%	
Hospital Mortality by Age	**≥50**	76	76.8%	84	74%	147	80%	p=0.526
	<50	23	23.2%	29	26%	37	20%	
ER Mortality by Age	**≥50**	34	79.1%	33	62.3%	62	84%	p=0.017
	<50	9	20.9%	20	37.7%	12	16%	

Table 2: Demographic comparison of hospital admissions in 2020 and COVID-19 suspected cases

		2020		Suspected COVID-19		p-value
Total Number of Admissions		395438		30229	7.6%	
Total ER Admissions		127293	32.2%	29174	96.5%	p=0.001
Total Hospital Mortality		184	0.1%	92	0.3%	p=0.001
Total ER Mortality		74	0.1%	16	0.1%	p=0.753
Hospital Mortality by Gender	**Female**	71	38.6%	33	35.9%	p=0.639
	Male	113	61.4%	59	64.1%	
ER Mortality by Gender	**Female**	29	39%	7	43.8%	p=0.681
	Male	45	61%	9	56.3%	
Hospital Mortality by Age	**≥50**	147	80%	78	84.8%	p=0.301
	<50	37	20%	14	15.2%	
ER Mortality by Age	**≥50**	62	84%	16	100%	p=0.011
	<50	12	16%	0	0%	

Table 3: Distribution of death causes by years

		Admission for Non-traumatic Cardiac Arrest of Unknown Cause	Malignancy	Respiratory Causes	Internal Causes	Surgical Causes	Neurological Causes	Traumatic Causes	Total
2018	**Count**	11	12	21	24	10	10	11	99
	%Year	11.1%	12.1%	21.2%	24.2%	10.1%	10.1%	11.1%	100.0%
2019	**Count**	13	16	24	22	10	9	19	113
	%Year	11.5%	14.2%	21.2%	19.5%	8.8%	8.0%	16.8%	100.0%
2020	**Count**	24	9	101	20	14	6	10	184
	%Year	13.0%	4.9%	54.9%	10.9%	7.6%	3.3%	5.5%	100.0%
		p=0.896	p=0.032	p=0.0001	p=0.038	p=0.803	p=0.077	p=0.017	

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DISCUSSION

Mortality analysis contains essential data in both country population and healthcare system evaluations (7). In this analysis, quality indicators and expected improvement potentials are determined (7). We analyzed hospital mortality during the COVID 19 pandemic, which is the subject of our study. In addition, we aimed to evaluate the effect of the COVID-19 pandemic on hospital admissions and in-hospital mortality from the first announcement of the pandemic in Turkey.

Although the number of overall hospital admissions was significantly decreased in 2020 compared to the same period of the previous two years in our study, there was a statistically significant increase in the rate of ER admissions. Of the 395438 patient admissions during this period, 127293 (32.2%) were ER admissions and 29174 (96.5%) of the 30229 suspected COVID-19 admissions. All suspected COVID-19 patients were admitted to ER; thus, it increased the rate of ER applications. In addition, we think that it is effective that patients do not apply to the hospital without severe complaints due to the risk of COVID-19 transmission. Similarly, Ensar&Fatih reported that ER applications decreased due to the COVID-19 pandemic close to our study period (8).

While there was an increase in overall hospital mortality rates, there was a significant decrease in deaths due to trauma, malignancy, and internal causes. The decreasing hospital admission could be due to the measures taken by the state against the COVID-19, such as curfews for specific age groups on weekends and at certain hours, restriction on the number of passengers in public transport, closure of shopping and entertainment centers, travel restrictions, providing formal education online. As well as increasing the follow-up of chronic patients in the healthcare system by family physicians, postponing all elective operations, hospital reorganization, warning of the public through the media frequently also had a positive impact on it. Accordingly, the number of patient admissions with a diagnosis other than COVID-19 has decreased. In support of this, Ensar&Fatih stated that the number of trauma cases applying to the ER during the pandemic period decreased significantly with the curfew (9).

Peter Wever et al. reported high mortality rates for ER and ICU, especially in 2020, COVID-19. In particular, they reported the ER mortality rate as 2.0% and the ICU mortality rate as 5.0% (10). In our study, the period of 01 March-30 June, which covers the first wave of the pandemic, was evaluated compared to the same period of the previous two years, and the mortality rates were lower than the mortality rates reported by this study. However, the ER and ICU mortality rates were increased in 2020, similar to this study. Therefore, it can be thought that the proportional difference between these studies may be the pandemic's peak in different regions.

It was found that the number of both in-hospital and ER deaths over 50 years was increased, especially in 2020. In the literature, studies conducted in China and Italy have emphasized that adults aged 65 and over have the highest mortality in terms of epidemiological characteristics (11–13). Even though overall hospital mortality under 50 years old was decreased in 2020, there was no statistical difference between the years. The analysis of the ER mortality revealed a significant decrease in the number of deaths under 50 years of age. Between our study dates, there were no ER deaths under 50 years of age with suspected COVID-19. We believe that the significant decrease in traumatic arrest cases may be due to the curfew restrictions within the scope of the measures taken in the COVID-19 pandemic, online education, and the reduction in vehicle traffic due to the transition to the flexible working system.

Yehia et al. emphasized that in the COVID-19 pandemic, the number of admissions of female cases was higher than that of males, but the male patients' mortality was 1.23 times more than females. Some other studies have emphasized that the male gender is a risk factor for deaths from COVID-19 disease (14, 15). Although our study supports these studies, there was a high rate of male deaths in years before the COVID-19 pandemic in our study, but it was not statistically significant.

When the mortality causes were analyzed for the three years evaluated within the scope of the study, it was notable that deaths occurred primarily due to respiratory causes in 2020. There was a notable increase in deaths due to respiratory causes in the three years and the current year 2020. As is known, COVID-19 disease presents with respiratory tract infection and progresses rapidly, and its mortality is higher than other respiratory tract infections (16, 17). Especially the involvement of the lower respiratory tract by the COVID-19 disease from the beginning and the development of multi-organ failure in the later period support the results of our study.

CONCLUSIONS

The Covid-19 pandemic has commenced meaningful changes in mortality rates and causes of mortality compared to previous years. However, the pandemic has affected all healthcare systems, especially ER and ICU. It is fundamental to improve inpatient and emergency healthcare services to decrease Covid-19 mortality.

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The effect of preoperative fasting to postoperative agitation, nausea, and vomiting in children with tonsillectomy

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ABSTRACT

Objective: This study was conducted to investigate the effect of the preoperative fasting period on postoperative agitation, nausea and vomiting in children with tonsillectomy.

Material and Methods: Children (n:123) who have had tonsillectomy between June and December 2017 and their families have taken place in the study. The data were collected by the researchers with a questionnaire. The questionnaire consists of 29 questions in total, including Watcha Behaviour Scale and Abramowitz Emesis Score.

Results: The mean duration of preoperative fasting was 11.03±1.17 hours, the duration of thirst was 10.17±1.00 hours. The mean Behaviour scores of the children were 1.28±0.27 points, the mean vomiting score of the children was 0.01±0.07 points, 56.9% of the children in the post-operative unit were not experiencing nausea. Between duration of pre-operative fasting with agitation and vomiting status in the postoperative unit was found to statistically no relationship. According to preoperative fasting time of children, a statistically significant difference was found when children were diagnosed as having or not having symptoms of nausea.

Conclusion: It was found that the children had longer duration of preoperative fasting than the guidelines suggested in the guidelines. It was observed that pre-operative fasting time did not affect postoperative agitation and vomiting, but it affected nausea.

Practice Implications: Surgical nurses should emphasize the importance of the fasting period to families before surgery and inform families on this issue.

Keywords: Child, fasting, nausea, vomiting, nursing

INTRODUCTION

Operations are a source of stress for the child and his/her family and it affects them physically, psychologically, socially and economically (1). Nurses have important duties in the preparation of children for surgery (2). During the planning of pre, intra and postoperative care of children, the development of the child and the impacts of surgery on the child and family should be known (3).

Preoperative evaluation and preparation are highly important for safe anesthesia and a successful surgical process. The preoperative preparation of the child includes clinical history, physical preparation, necessary examinations, informing patients and their parents and psychological preparation of them (4). One of the preoperative physical preparations is preoperative fasting. The purpose of preoperative fasting is to prevent aspiration of stomach contents into the lung, especially during induction (3,4,5).

Preoperative fasting is achieved under the control of nurses in the hospital, whereas it is considered as the responsibility of families in outpatient surgery (3). In various countries, guidelines have been prepared for preoperative fasting periods. These guides recommend 2-hour preoperative fasting for clear fluids and 6-hour fasting for solid foods (6-15). However, in the studies, the preoperative fasting periods are longer than those recommended in the guidelines (3, 16-19).

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Prolonged preoperative fasting period may cause negative effects such as the feeling of hunger, discomfort, headache, dehydration, hypovolemia, and hypoglycemia (4, 17). In addition, prolonged preoperative fasting may cause a decrease in satisfaction, lead to nausea, vomiting, crying, discomfort in the postoperative period, thus to failures in the healing process and late discharge (3, 6, 16, 20). Not-Prolonged preoperative fasting allows children to feel better and experience less surgical stress (1, 2, 3).

Prolonged preoperative fasting can cause stress in children (3). This may cause Behavioural changes such as delirium and agitation in children in the postoperative care unit (21, 22). This short-term Behaviour disorder can lead to distress in the child, his/her family, and the care-giving personnel and may cause dissatisfaction with anesthesia. Additionally, because of these Behaviours, children can dislocate their cannula, dressings, and catheters (23). Moreover, swallowing difficulty, pain nausea and vomiting experienced after a tonsillectomy may make this process difficult (24). Considering all these, a good pre-operative preparation by nurses can prevent postoperative complications or control those that may occur (1, 2).This study was conducted to investigate the effect of preoperative fasting period on postoperative agitation, nause and vomiting in children with tonsillectomy.

MATERIAL and METHODS

This descriptive and cross-sectional study was conducted in the recovery unit of the Otorhinolaryngology Department Operating Room in a University Hospital between June-December 2017. The universe of the study consisted of children aged 4-13 years who were in the recovery unit between June and December 2017 and who underwent tonsillectomy (n: 567) and the sample of the study consisted of children aged 4-13 years who were in the recovery unit between June and December 2017, who underwent tonsillectomy, who volunteered to participate in the research, and who were able to communicate and their families (n: 123).

The data were collected from the children, their mothers in face to face interviews, and patient files using the data collection form created by the researchers. This form was prepared by the researchers reviewing the relevant literature in order to determine the sociodemographic and clinical characteristics of children. The form consists of 29 questions in total, including four questions regarding sociodemographic characteristics of children, ten questions regarding preoperative conditions, five questions regarding intraoperative conditions, and ten questions regarding postoperative conditions. The children were asked to evaluate their feelings of hunger and thirst between 0 and 10 points. Their agitation status was assessed using the Watcha Behaviour Scale (25, 26) and the emesis status was evaluated using the Abramowitz Emesis Scoring Scale (27). The Watcha Behaviour Scale is a four-point scale. According to the scale, 1 point is interpreted as calm, 2 points as crying but can be consoled, 3 points as crying, not consoled, 4 points as agitated and thrashing around (25, 26). The Abramowitz Emesis Score, created by M.D. Abramowitz et al., is a scoring system for nausea and vomiting used in postoperative recovery units for both adults and children. The scoring according to the Abramowitz Emezis Score is as follows; score 0: no vomiting; Score 1: mild vomiting, once per observation period; Score 2: moderate vomiting, two or three times per observation period; Score 3: severe vomiting, four or mor eper observation period; Score 4: persistent vomiting regardless of treatment (27).

The data of the research were evaluated using the Statistical Package for Social Science (SPSS) 18 package program. In the evaluation, number, percentage distributions, mean, minimum, maximum, standard deviation, Mann Whitney U tests and Spearman Correlation tests were used. The normal distribution of the data was analysed using the Kolmogorov Smirnov test. The data were evaluated at a 95% confidence interval. Statistical significance was accepted to be 0.05.

After obtaining permission from the Scientific Research and Publication Ethics Committee of a University (date: 20 April 2017 protocol number: 118-2017) in order to carry out the study, written permission was obtained from the institution where the research was conducted. The consent of the children and their mothers was taken using informed consent forms.

RESULTS

The socio-demographic characteristics of the children included in the study are given in **Table 1**. The mean age of the children was 9.76±1.74 years (min:6.0-max:13.0).

Table 1: Distribution of Children according to their socio-demographic characteristics

	Number	Percentage
Age		
6 years old	4	3.3
7 years old	12	9.7
8 years old	14	11.4
9 years old	17	13.8
10 years old	35	28.5
11 years old	19	15.4
12 years old	7	13.8
13 years old	5	4.1
Gender		
Male	56	45.5
Female	67	54.5
Education		
Kindergartens	4	3.3
Primary School	119	96.7
Area of living		
City	28	22.8
District	95	77.2
Total	**123**	**100.0**

It was found that all the children spend the night before surgery at home. It was determined that all families were informed about the nutrition of children before surgery, that the information was given by their doctors, and that no written material was provided. It was found that 8.9% of children fasted 9 hours; 23.6% fasted 10 hours; 35.8% fasted 11 hours; 21.1% fasted 12 hours; 8.9% fasted 13 hours; 0.8% fasted 14 hours; 0.8% fasted 15 hours. Children's mean preoperative fasting time was 11.03 ± 1.17 (min:9.0-max:15.0) hours. It was seen that, according to the ASA

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classification, 3.3% of the children consumed particulate liquids (soup, etc.); 82.1% consumed solid foods; 14.6% consumed fatty-hard-to-digest food before surgery.

29.3% of the children were dehydrated for 9 hours; 35% were dehydrated for 10 hours; 26.0% were dehydrated for 11 hours; 8.1% were dehydrated for 12 hours; 1.6% were dehydrated for 13 hours. Children's mean preoperative dehydration time was 10.17 ± 1.00 (min:9.0-max:13.0) hours. Children's last drinks before surgery were distributed according to ASA classification. 77.2% of the children drank water and 22.8% drank milk or fruit juice.

The preoperative fasting level was scored between 0 and 10 points and it was determined that 3.3% of the children gave 6 points; 28.5% gave 7 points; 51.2% gave 8 points; 16.3% gave 9 points; 0.8% gave 10 points. Children's mean preoperative fasting level was 7.82 ± 0.76 (min:9.0- max: 10.0).

The preoperative dehydration level was scored between 0 and 10 points and it was determined that 12.2% of the children gave 6 points; 35.8% gave 7 points; 38.2% gave 8 points; 11.4% gave 9 points; 2.4% gave 10 points. Children's mean preoperative dehydration level was 7.56±0.93 (min:6.0-max:10.0).

Children's mean duration of surgery was 68.17 ± 12.51 (min:45.0- max:105.0) minutes. The mean duration of mothers' admission to the recovery unit was 6.95 ± 5.18 (min:0.0- max:20.0) minutes. Children's mean duration of stay in the recovery unit was 48.17 ± 6.99 (min:30.0 - max:60.0) minutes.

It was found that children's mean Watcha Behaviour scale score was 1.28 ± 0.27 (1.00-2.67), that the lowest mean was seen at the 60th minute with 1.00 points, and that the highest mean was seen at the 0th minute with 1.78 points.

It was found that children's mean Abramowitz emesis score was 0.01 ± 0.07 (0.00-0.40), that the lowest mean was seen at the 30th, 45th and 60th minute with 0.00 point, and that the highest mean was seen at the 0th minute with 0.07 points.

It was observed that, in the recovery unit, 43.1% of the children experienced nausea and 56.9% did not experience. Children's mean duration of nausea in the recovery unit was 13.30 ± 10.17 (0.00-30.00) minutes.

The children's mean duration of hospital stay was 5.25 ± 0.75 (4.00-7.00) hours.

There was no statistically significant correlation between children's preoperative fasting time and the agitation status (Watcha Behaviour Scale) in the recovery unit (rs: -0.064; p:0.481) and between preoperative fasting time and vomiting status (Abramowitz Emesis Score) (rs: -0.064; p:0.483) (**Table 2**).

There was no statistically significant correlation between the duration of surgery and the agitation status in the recovery unit (Watcha Behaviour Scale) (rs: 0.043; p: 0.634) and between the duration of surgery and the vomiting status in the recovery unit (rs: 0.060; p: 0.513) (**Table 3**).

Table 2: The correlation of Children's Preoperative Fasting Time with Agitation Status (Watcha Behaviour Scale) and Vomiting Status (Abramowitz Emesis Score) in the Recovery Unit (n: 123)

		Fasting Time (Hour)	Mean Watcha Behavior Scale Score	Mean Abromowitz Emesis Scale Score
Fasting Time	rs	1.000	-0.064	-0.064
(Hour)	p	-	0.481	0.483
Mean Watcha Behaviour	rs	-0.064	1.000	0.372**
Scale Score	p	0.481	-	0.001
Mean Abromowitz	rs	-0.064	0.372**	1.000
Emesis Scale Score	p	0.483	0.001	-

rs : Spearman Correlation Analysis, * p<0.05 ** p<0.01

Table 3: The correlation of Children's Duration of Surgery with Agitation Status (Watcha Behavior Scale) and Vomiting Status (Abramowitz Emesis Score) in the Recovery Unit (n: 123)

		Duration of Surgery Min)	Mean Watcha Behavior Scale Score	Mean Abromowitz Emesis Scale Score
Duration of Surgery	rs	1.000	0.043	0.060
(Min)	p	-	0.634	0.513
Mean Watcha Behavior	rs	0.043	1.000	0.372**
Scale Score	p	0.634	-	0.001
Mean Abromowitz	rs	0.060	0.372**	1.000
Emesis Scale Score	p	0.513	0.001	-

rs : Spearman Correlation Analysis, * p<0.05 ** p<0.01

There was a statistically positive weak correlation between the duration of stay in the recovery unit and agitation status (Watcha Behaviour Scale) (rs: 0.269; p: 0.003) (Table 4). As a result, as the duration of stay in the recovery unit increased, the score obtained according to the Watcha Behaviour Scale and agitation increased, as well.

There was a statistically positive weak correlation between the duration of stay in the recovery unit and the vomiting status (Abramowitz Emezis Score) in the recovery unit (rs: 0.276; p: 0.002) (**Table 4**).

There was a statistically negative moderate correlation between the age and agitation status of children (Watcha Behaviour Scale) (rs: -0.476; p: 0.001). As a result, it was determined that as the child's age increased, the score obtained according to the Watcha Behaviour Scale decreased and the child calmed down. There was no statistically significant correlation between the age and vomiting status of children (Abramowitz Emesis Score) (rs:-0.134; p:0.140).

When the agitation status (Watcha Behaviour Scale) of the children was analysed according to sex, a statistically significant difference was found (z:-2.130, p:0.033). As a result, it was observed that girls got more agitated than boys. When the vomiting status (Abramowitz Emesis Score) of the children was analysed according to sex, there was no statistically significant difference found (z:-0.141, p: 0.888).

When the nausea status of children was analysed according to their preoperative fasting time, there was a statistically significant difference was found (z: -2.115, p: 0.034) (**Table 5**). The mean fasting time of the children who had nausea was 10.7 hours whereas the mean fasting time of the children who did not have nausea was 11.2 hours.

When the nausea status of children was analysed according to the duration of surgery, there was no statistically significant difference (z: -1.821, p: 0.069) (Table 5). The mean duration of surgery of the children who had nausea was 70 minutes and the mean duration of surgery of the children who did not have nausea was 66 minutes.

When the nausea status of children was analysed according to the duration of stay in the recovery room, there was a statistically significant difference found (z: -3.508, p: 0.001). It was found that the children who had nausea had a longer stay in the recovery unit whereas the children who did not have nausea had a shorter stay in the recovery unit.

There was no statistically significant correlation between the duration of mothers' admission to the recovery unit and agitation status (Watcha Behaviour Scale) (rs: -0.149; p: 0.099). There was no statistically significant correlation between the duration of mothers' admission to the recovery unit and vomiting status in the recovery unit (Abramowitz Emesis Score) (rs: 0.040; p: 0.661).

Table 4: The correlation of Children's Duration of Stay in the Recovery unit with Agitation Status (Watcha Behavior Scale) and Vomiting Status (Abramowitz Emesis Score) (n: 123)

		Duration of Stay in the Recovery Unit (Min)	Mean Watcha Behavior Scale Score	Mean Abromowitz Emesis Scale Score
Duration of Stay in the Recovery Unit (Min)	rs	1.000	0.269**	0.276**
	P	-	0.003	0.002
Mean Watcha Behavior Scale Score	rs	0.269**	1.000	0.372**
	P	0.003	-	0.001
Mean Abromowitz Emesis Scale Score	rs	0.276**	0.372**	1.000
	p	0.002	0.001	-

rs : Spearman Correlation Analysis, * p<0.05 ** p<0.01

Table 5: Comparison of Children's Nausea Status According to Preoperative Fasting Time, Duration of Surgery, Duration of Stay in the Recovery Unit (n: 123)

	Nausea	n	Mean ± SD (min-max)	z	p*
Fasting Time (Hour)	Yes	53	10.792 ± 0.15(9.00-14.00)	-2.115	0.034
	No	70	11.214 ± 0.14(9.00-15.00)		
Duration of Surgery (Min)	Yes	53	70.755 ± 1.82(45.00-90.00)	-1.821	0.069
	No	70	66.214 ± 1.38(45.00-105.00)		
Duration of Stay in the Recovery Unit (Min)	Yes	53	50.660 ± 1.08(30.00-60.00)	-3.508	0.001
	No	70	46.286 ± 0.66(30.00-60.00)		

* Mann Whitney U test, Mean: Arithmetic mean, SD: Standard deviation, Min: Minimum value, Max: Maximum value

DISCUSSION

Analysis of distribution of children according to their descriptive characteristics

Tonsillectomy is one of the most commonly applied procedures in children. The frequency of tonsillectomy varies according to geographical characteristics, medical developments, experts who decide on the intervention, and differences in sociocultural characteristics (**28**).

In the study, the mean age of the children was found to be 9.76 ± 1.74 (min:6.00-max:13.00). 54.5% of the children were female; 96.7% were in primary school; 77.2% lived in a district. In the study conducted by Polat et al. in 2010 with 413 children, it was found that 59% of the children were male and that the mean age of the cases was 13.3 ± 3.8 years (**28**). In the study conducted by Gülbetekin with 68 children aged

6-17 years who underwent a tonsillectomy, it was found that 60.2% of the children were male and that 47% were at the age of 7-11 years (29).

Analysis of distribution of children according to their preoperative information

It was seen that all of the children spent their last nights before surgery at home and that the necessary information about preoperative nutrition was given by their doctors verbally. It was determined that the children and their relatives did not receive a written document. In the study conducted by Dolgun et al. about preoperative fasting, it was observed that 97.6% of the patient relatives were informed about preoperative nutrition (3). The aim of preoperative patient training is to prevent complications and teach the necessary knowledge and skills to the patient. Preoperative training provided before the surgical intervention contributes to the patient's knowledge of what will happen at each stage of the surgical intervention, makes the patient feel better physically and spiritually and to get positive surgical results. It is recommended to use visual and written materials (2). Nurses who give care to patients the most must identify the needs of patients and their relatives, inform them, and help them cope with difficulties. In the study, it was seen that the information was given by doctors.

It was found that the mean preoperative fasting time of the children was 11.03 ± 1.17 (min 9.0- max:15.0) hours, that 82.1% consumed solid food before fasting, and that the mean dehydration time was 10.17 ± 1.00 (min:9.0-max:13.0) hours, and that 77.2% drank water before fasting. Preoperative fasting guidelines have been designed to reduce the risk of pulmonary aspiration of gastric contents by reaching into the lungs during general anesthesia. In this context, the appropriate fasting time has been determined to be 6-8 hours for solids, 4 hours for particulate fluids, 4 hours for breast milk, and 2 hours for clear fluids (7-15). In this study, it was seen that the fasting and dehydration periods were longer than those recommended in the guidelines. It was found that the mean fasting level of the children was 7.82 ± 0.76 (min:9.0-max:10.0) point and that the mean dehydration level was 7.56 ± 0.93 (min:6.0- max:10.0) point. The mean fasting and dehydration scores of the children were similar to those in the literature (3, 16). In the study conducted by Engelhardt with 1350 children in 2011, 56% of the children stated that they were starving and 27% stated that they were very thirsty. In this study, it was determined that children who underwent outpatient surgery had significant discomfort before the surgery due to excessive hunger and thirst (17). Regarding fasting, patients in our country are told to limit consuming solid food or fluids after 00:00 at night. Therefore, it is suggested that fasting and dehydration times are long and that there is a need for arrangements to ensure appropriate preoperative fasting times.

Analysis of distribution of children according to their intraoperative information

It was determined that children's mean duration of surgery was 68.17 ± 12.51 (min: 45.0- max:105.0) minutes and that the mean duration of stay in the recovery unit was 48.17 ± 6.99 (min: 30.0- max:60.0) minutes. The mean duration of mothers' admission to the recovery unit was 6.95 ± 5.18 (min: 0.0- max:20.0) minutes. Patients who have regular vital signs, who are conscious, who have place-time-person orientation, who have adequate urine output, and who do not have nausea-vomiting, pain and abnormal flows from drains are taken to the service after the recovery unit, here the recovery process is monitored, and the patient is prepared for home care (30). Being in a foreign environment and away from the mother is among the conditions that cause anxiety and agitation (31). In this case, it is important to take mothers into the recovery unit to be with their children in the early period. In the study, it was seen that mothers were taken to the recovery unit very early.

Analysis of distribution of children according to their postoperative information

In the study, the Watcha Behaviour Scale scores of children were evaluated at 0th, 15th, 30th, 45th and 60th minutes and the mean score was found to be 1.28 ± 0.27 (1.00-2.67). According to the Watcha Behaviour Scale, 1 point refers to calm, 2 points to crying but can be consoled, 3 points to crying and cannot be consoled, 4 points to agitated and trashing around (25, 26). In the study, it was observed that the 0th-minute mean score of the children was 1.78 ± 0.59 (1.00-3.00) points and the mean score decreased at 60th minute to 1.00 ± 0.00 (1.00-1.00). Children were in a state that they were calm and crying, but they could be consoled. In the study conducted by Bajwa et al. in 2010 with 117 children below 18 years of age, the agitation of 30 children in the recovery unit was evaluated using the Watcha Behaviour Scale, and it was found that 26% of the children were agitated (25). In the study, the vomiting status of the children was evaluated at 0th, 15th, 30th, 45th and 60th minutes. The mean score was 0.07± 0.29 (0.00-2.00) points at 0th minute, 0.01± 0.12 (0.00-1.00) points at 15th minute, and 0.00± 0.00 (0.00-0.00) at other times. According to the Abromowitz Emesis score, 0 point indicates no vomiting and 1 point indicates mild vomiting (1 time) (27). In this case, it was seen that the mean vomiting at the 0th and 15th minutes was very low in the study and that no vomiting was seen in the recovery unit after the 15th minute. It was determined that 56.9% of children did not have nausea in the recovery unit. The mean duration of nausea was 13.30 ± 10.17 (0.00-30.00) minutes in those who had nausea. Nausea and vomiting are among the most common postoperative complications. Many factors can affect nausea and vomiting besides the surgical procedure and the operation area (30). Therefore, it is important for the nurse to evaluate the patient systematically and apply appropriate nursing interventions to prevent nausea and vomiting.

It was determined that children's mean duration of hospital stay was 5.25 ± 0.75 (4.00-7.00) hours. Outpatient surgery is more preferred for children. In outpatient surgery, children come from their homes with their families in the morning, and they return home after the surgery the same day with their families (32). With outpatient surgery, the duration of separation from the family is shortened and the risk of getting hospital infections decreases (32). Therefore, the early discharge of children is important.

Examination of the correlation between preoperative and postoperative conditions of children

In the study, there was no significant correlation found between preoperative fasting times and agitation in the recovery unit and between preoperative fasting times and

vomiting. In the survey conducted by Klemetti et al. in 2009, in which children underwent an outpatient tonsillectomy, the control group received routine information, and the study group received nutritional counselling. The mean last solid food intake times were similar, whereas the mean fluid intake time was 2.69 (2.08), 1.91/14.35 hours in the study group and 12.13 (2.45), 2.95/14.05 hours in the control group. The difference in the frequency and intensity of postoperative nausea and vomiting between the study and control groups was not statistically significant (**33**). In the study conducted by Jayasinghe et al. in 2018 with 404 children who will undergo bone marrow aspiration, children were divided into two groups randomly; one group fasted for more than 3 hours, and the other group fasted 3 hours. 15.8% of the children in the fasting group and 8.4% of the non-fasting group experienced vomiting in the postoperative period, and excessive hunger was determined to be a risk for vomiting after paediatric anaesthesia (**34**).

In the study, there was no statistically significant correlation found between the duration of surgery and agitation and vomiting status in the recovery unit. There was a statistically weak correlation found between the duration of stay in the recovery unit and agitation and vomiting status in the recovery unit. As a result, it was determined that the agitation of children increased as the duration of the stay in the recovery unit increased. It is thought that agitation may be affected by being in a foreign environment for a long time.

In this study, it was seen that agitation decreased as the age of the children increased and that girls got more agitated than boys. In the study conducted by Uğur et al. in 2018, in which the factors affecting the recovery agitation of paediatric patients between the age of 3-10 were investigated, it was stated that age significantly affected agitation. The agitation score was high in children below the age of 6 years but decreased towards the age of 10 (**35**).

In the study, the mean fasting time of the children who had nausea was 10.792 ± 0.15 (9.00-14.00) hours whereas the mean fasting time of the children who did not have nausea was 11.214 ± 0.14 (9.00-15.00) hours and the difference was found to be statistically significant. The mean duration of surgery was 70 minutes for the children who had nausea and 66 minutes for those who did not have nausea. It was found that the children who had nausea stayed longer in the recovery unit whereas the children who did not have nausea stayed shorter stay in the recovery unit. In the study conducted by Klemetti et al., the frequency and intensity of postoperative nausea and vomiting were not found to be statistically significant between the study group who received nutritional counselling and had a shorter fluid intake time and the control group (**33**). There was no significant correlation found between the duration of mothers' admission to the recovery unit and agitation and vomiting. The fact that the mothers were taken inside as soon as possible may be effective in the results.

CONCLUSIONS

It was seen that the fasting time of the children was longer than those recommended in the guidelines, that the preoperative fasting time did not affect the postoperative agitation and vomiting status and affected the nausea status. It was determined that there was a correlation between children's age and agitation, and that sex affected agitation.

It may be recommended to increase the awareness of nurses about the fasting periods of the children and ensure them to take an active role in preoperative preparation, to use written materials to inform children and their families about preoperative preparation, to keep children as short as possible in the recovery unit after surgery, and to enrich the relevant literature by carrying out studies on agitation with different groups and larger samples.

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