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Evaluation of Demographic and Laboratory Parameters of Acute Coronary Syndrome Cases During and Before the COVID-19 Pandemic

Akut Koroner Sendrom Olgularının COVID-19 Pandemisi Sırasında ve Öncesinde Demografik ve Laboratuvar Parametrelerinin Değerlendirilmesi

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Abstract

Objective: Both ischemic heart diseases and Coronavirus disease-2019 (COVID-19) are the two main patient groups who frequently apply to emergency clinics recently. We aimed to evaluate the impact of the COVID-19 pandemic on the demographic and clinical processes in acute coronary syndrome (ACS) cases.

Method: This retrospective, single-center study was conducted on ACS patients who applied to the emergency department between March 10, 2019 and March 11, 2021. While the patients were divided into two as pandemic and prepandemic, the pandemic period was also grouped as COVID (+) and (-). ACS classification, clinical and laboratory results of the patients were evaluated.

Results: The mean age of 1.067 patients included in the study was 58.0±19.2 years and 785 (73.5%) were male. Two hundred and sixty-two (48.3%) of 542 cases in the pre-pandemic period were non-ST myocardial infarction (NSTEMI) and 202 (37.3%) were ST elevated myocardial infarction (STEMI). Among the COVID (+) cases in the pandemic group, 194 (76.9%) of 252 patients were NSTEMI and 34 (13.6%) were STEMI (p=0.001, p=0.013). During the pandemic period, STEMI was responsible for 7 (87.5%) of the 8 deaths in the COVID (-) group. In contrast, 20 (77%) of 26 COVID (+) deaths occurred in the NSTEMI group. NSTEMI mortality was considerably greater in the COVID (+) group (p=0.001).

Conclusion: Rapid care of instances of ACS in the emergency department has an effect on patient outcomes. Determining the severity, risk factors, laboratory findings, and outcomes of COVID-19 disease is crucial for a complete understanding of the mechanisms that can induce

Öz

Amaç: Hem iskemik kalp hastalıkları hem de Koronavirüs hastalığı-2019 (COVID-19) son dönemlerde acil servislere sıklıkla başvuran iki ana hasta grubunu oluşturmaktadır. Akut koroner sendrom (AKS) olgularında COVID-19 pandemisinin demografik ve klinik süreçlere etkisini değerlendirmeyi amaçladık.

Yöntem: Bu retrospektif, tek merkezli çalışma, 10 Mart 2019-11 Mart 2021 tarihleri arasında acil servise başvuran AKS hastaları üzerinde yapılmıştır. Hastalar pandemi ve prepandemi dönemi olarak ikiye ayrılırken, pandemi dönemi de COVID (+) ve (-) olarak gruplandırıldı. Hastaların AKS sınıflaması, klinik ve laboratuvar sonuçları değerlendirildi.

Bulgular: Çalışmaya alınan 1,067 hastanın yaş ortalaması 58,0±19,2 yıl ve 785'i (%73,5) erkekti. Pandemi öncesi dönemdeki 542 olgunun 262'si (%48,3) non-ST elevasyonlu miyokard enfarktüsü (NSTEMI) ve 202'si (%37,3) ST elevesyanlu miyokard enfarktüsü (STEMI) idi. Pandemi grubundaki COVID (+) olgularından 252 hastanın 194'ü (%76,9) NSTEMI ve 34'ü (%13,6) STEMI idi (p=0,001, p=0,013). Pandemi döneminde COVID (-) grubundaki 8 ölümün 7'si (%87,5) STEMI kaynaklıydı. Buna karşılık 26 COVID (+) ölümün 20'si (%77) NSTEMI grubunda izlendi. NSTEMI mortalitesi COVID (+) grubunda önemli ölçüde daha yüksekti (p=0,001).

Sonuç: Acil serviste AKS olgularının hızlı değerlendirilmesi hasta hasta prognozu üzerinde oldukça etkilidir. COVID-19 hastalığının ciddiyetinin, risk faktörlerinin, laboratuvar bulgularının ve sonuçlarının doğru değerlendirilmesi, şiddetli akut solunum sendromu-koronavirüs-2 enfeksiyonunda AKS indükleyebilecek mekanizmaların tam olarak

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Abstract

ACS in severe acute respiratory syndrome-coronavirus-2 infection and for the development of strategies to facilitate the diagnosis and transfer of treatment in these patients.

Keywords: Acute coronary syndrome, COVID-19, emergency department, mortality

Öz

anlaşılması, tanı ve tedaviyi kolaylaştıracak stratejilerin geliştirilmesi açısından oldukça önemlidir.

Anahtar kelimeler: Acil servis, akut koroner sendrom, COVID-19, mortalite

Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity among adults despite modern medical facilities (1). In acute coronary syndromes (ACS), cardiovascular pathologies require rapid evaluation due to the importance of early diagnosis and treatment (2). In ACS cases, diagnosis and initiation of treatment in the emergency department is a critical dynamic process (3). Not promptly initiating appropriate treatments (cardiovascular and metabolic stability, emergency thrombolysis, oral antiaggregant, anticoagulant treatments or percutaneous interventions) for patients presenting to the emergency department with ACS results in a poor prognosis, and seriously affects morbidity and mortality (4). Negligence and disruptions in this process cause negativities in the health system and high cost rates in economic terms (5).

The emergence of the Coronavirus disease-2019 (COVID-19) pandemic has affected rates of ACS cases and changed the use of healthcare resources worldwide (6). At the onset of the pandemic, invasive cardiac procedures were primarily performed only in cases of ST-segment elevation myocardial infarction (STEMI) and critically non-ST-segment myocardial infarction (NSTEMI) to minimize personnel exposure (7). Considering the change in the application rates made with ACS during the pandemic period, different results were obtained according to the countries (8-10). NSTEMI cases were found to have a higher incidence of MI (45%) with non-obstructive coronary arteries compared to pre-pandemic cases, and this was suggested to be due to the inflammatory role of COVID-19 on acute coronary arteries (11). In a study conducted in Italy, one of the countries most affected during the pandemic, a decrease in STEMI rates was found (12). It has become important to determine patient response during the COVID-19 pandemic and its impact on acute medical conditions such as acute myocardial infarction.

During the COVID-19 pandemic, a sudden decrease in hospitalizations and an increase in out-of-hospital deaths were observed with ACS (13,14). The increase in mortality rates in ACS patients with concomitant COVID-19 was considered to be associated with acute myocardial injury secondary to novel Coronavirus 2019 severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (11). Rapid adaptation of the existing emergency health operation was necessary for overloaded healthcare systems to manage both a new transmission and an existing disease (15). Well-designed prognostic studies in the light of retrospective studies are required to better define the complex interaction of COVID-19 infection and cardiovascular disease caused by SARS-CoV-2.

Thus, it was aimed to contribute to the literature by showing the effect of COVID-19 disease on ischemic heart diseases.

Materials and Methods

Study Design and Population

Our retrospective, single-center study was conducted on patients who applied to our tertiary education and research hospital emergency department between March 10, 2019 and March 11, 2021. The study date range was planned according to the period declared as a pandemic in our country. The groups were divided into pre-pandemic (10.03.2019-10.03.2020) and pandemic (11.03.2020-11.03.2021). Comparisons made during the study were made between the pre-pandemic and the pandemic period. In total, 1.795 patients associated with cardiovascular diseases were studied. Patients diagnosed with STEMI, NSTEMI and unstable angina pectoris (USAP), which are the ACS groups, were selected. A total of 1.067 patients over the age of 18 (mean age 58.6±12.4 years, range 19-96 years) who met the definition of ACS were included in the study. For the definition of ACS, the codes specified in the International Classification of Diseases-10 (ICD-10) international disease coding system [ICD-10 codes for (USAP) (I20.0), STEMI (I21.0, I21.1, I21.2, and I21.3), NSTEMI (I21.4 and I22.2)] were used. Patients over the age of 18, who had complete demographic and laboratory data in the hospital data recording system, gave consent in accordance with the law on personal data protection,

and did not have additional pathologies specified in the exclusion criteria, were included. Among the data obtained from the hospital registry system, patients diagnosed other than ACS, who had recurrent records due to transfer within the cardiology clinic, and whose file information could not be accessed were excluded from the study. Patients diagnosed in the hospital registry system but with erroneous or insufficient test results, patients whose laboratory tests were requested in the hospital registry system but left the hospital without permission, additional disease (non-COVID infection, chronic systemic inflammatory disease, cerebrovascular disease, chronic liver failure). Patients with a history of anemia and haematological diseases, transfusion administration in the last 6 months) were excluded from the study.

Pandemic patients were divided into two groups as COVID (+) and COVID (-). Real-time polymerase chain reaction positivity was used to determine the diagnosis of COVID-19 infection. Age, gender, history, white blood cell (WBC), neutrophil, lymphocyte, thrombocyte, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) values and mortality status of the patients were analyzed. Hemogram blood was measured using Sysmex DI-60 CBC Analyzer (İstanbul, Turkey). Hemogram results were studied in 30-45 minutes.

The study was conducted after the Declaration of Helsinki for Human Research and was approved by the local ethical review board. Ethics committee approval was obtained from the Local Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (E-10840098-772.02-1405, 21.03.2021).

Statistical Analysis

IBM SPSS Statistics 18© (Copyright SPSS Inc. 1989, 2010) software was used for statistical analysis in our study. Frequencies were determined by performing descriptive statistical analyzes on all of the data. Categorical variables were expressed as frequency (n) and percentage (%), and continuous variables as mean ± standard deviation (SD). Comparative statistical analyzes were determined using independent Student's t-test and chi-square test, depending on the type of variable. Results statistical analyzes were performed based on $p<0.05$ significance level and 95% confidence interval.

Results

The mean age of 1.067 patients included in the study was 58.0±19.2 years and 785 (73.5%) were male. Of the 542 patients in the pre-pandemic period, 405 (74.7%) were male and 137 (25.3%) were female. In the pandemic group, 201 (73.6%) of the COVID (-) cases and 179 (71%) of the COVID (+) cases were male. The mean ages of the groups were 56.3±21.1, 56.5±20.2, and 63.3±15.1 years, respectively, in the prepandemic, pandemic COVID (-), and pandemic COVID (+) periods (Table 1).

While 262 (48.3%) of 542 cases in the pre-pandemic period were NSTEMI and 202 (37.3%) were STEMI; among the COVID (+) cases in the pandemic group, 194 (76.9%) of 252 patients were NSTEMI and 34 (13.6%) were STEMI (p=0.001, p=0.013). USAP cases constituted 78 (14.4%) cases in the pre-pandemic period and 76 (14.5%) of 525 cases in the pandemic period. It was observed that USAP did not differ significantly between the groups (Table 2).

ACS diagnoses and Hb, WBC averages of the patients were compared. PD Hb values were 13.52±1.7 WBC values were 9.8±2.7, in PD Hb values were 14.01±1.9, WBC values, were 9.9±3.1. No significant difference was observed between the groups (p=0.843, p=0.921). ACS diagnoses and Hb, WBC averages of patients diagnosed with COVID-19 were compared. The Hb values of patients without a diagnosis of COVID-19 are 13.66±1.9. WBC values 9.48±2.8. In patients diagnosed with COVID-19, Hb values were measured as 13.68±2.1 and WBC values as 10.49±3.4. No significant difference was observed between the groups (p=0.961, p=0.991). The levels of C-reactive protein (CRP), troponin, and D-dimer were evaluated and found to have substantial SDs and variances. Variations may have come from variations in patients' arrival times at the hospital.

NLR and PRL values of the patients were 2.91±2.5 and 116.5±70.4, respectively, in the prepandemic group, 2.47±1.8 and 110.1±48.4 in NSTEMI, 3.49±2.5 and 125.8±76.4 in STEMI patients, respectively. While these values were similar in COVID (-) cases during the pandemic period, they were determined as 3.2±2.7 and 125.9±82.7 in NSTEMI, 4.1±3.2 and 159.8±80.7 in STEMI in cases with COVID-19(+). NLR and PLR rates in COVID-19(+) cases showed statistically significant differences in NSTEMI and STEMI types (p=0.027, p=0.039, Table 3).

Considering the comorbidity rates in COVID-19 (+) patients, 144 (63.7%) of 226 COVID (+) patients had a history of coronary artery disease (CAD) (p=0.001).

Three of the 4 cases (75%) that resulted in mortality in the pre-pandemic period were in the STEMI group. During the pandemic period, 7 (87.5%) of 8 cases in the COVID (-) group with mortality were STEMI. On the other hand,

20 (77%) of 26 patients in COVID (+) deaths were in the NSTEMI group. Mortality with NSTEMI was significantly higher in the COVID (+) group (p=0.001, Table 4).

Discussion

Despite all possibilities of modern medicine, today ischemic heart diseases are one of the leading causes of morbidity and mortality in adults (16,17). In countries where there are more cardiologist and percutaneous coronary intervention centers than the population, the fact that factors such as diabetes mellitus, smoking and obesity increase the mortality in ischemic heart diseases (18). It has been shown that in addition to social factors such as age, gender and lifestyle as the main risk factors in ischemic heart diseases, infectious diseases such as pneumonia lead to an increase in ischemic disease rates (19,20).

The relationship between the increase in mortality rates in the COVID-19 disease pandemic process, which was announced after the pneumonia cases that started in China in December 2019, and later spread to the whole world, with other diseases has been the subject of many studies (21-23). It has become important to reveal the relationship between COVID-19 and cardiovascular pathology, since the mortality rates of COVID-19 are higher in patients with cardiovascular pathology and the severity of COVID-19 is associated with cardiovascular symptoms (24). Making updates for the early diagnosis and intervention of patients with ACS during the COVID-19 process has also been the subject of international cardiology societies (25). Reduction or delay in hospital admissions of patients with ACS during the pandemic, differential diagnosis of acute myocardial injury, hospital isolation and protection of healthcare workers constituted the main difficulties experienced during the pandemic process (26). Considering gender predisposition, it was observed that male rates were higher in COVID-19 patients in previous studies (27). Susceptibility to COVID-19 infection was observed more in European countries in women before 50 years of age (28). On the other hand, it has been determined that in all age groups, men are hospitalized 20% more due to COVID-19 disease, need intensive care, and mortality is 1.74 times higher than women (27). It is suggested that the reason for the high mortality and morbidity rates observed in men is that they have more risk factors due to high smoking, stress and susceptibility to infection (29,30). In all patients examined

Table 1. Female and male application rates and mean ages prior to and during the influenza pandemic

	Pre-pandemic	**Pandemic**		**Total**
Gender	n (%)	COVID-19 (-) n (%)	COVID-19 (+) n (%)	
Male	405 (74.7)	201 (73.6)	179 (71)	785 (73.5)
Female	137 (25.3)	72 (26.4)	73 (29)	282 (26.5)
Total	542 (100)	273 (100)	252 (100)	1067 (100)
Mean age	**Mean ± SD**	**COVID-19 (-) Mean ± SD**	**COVID-19 (+) Mean ± SD**	
Male	56.6±21.2	55.4±20.5	61.6±14.9	57.4±16.5
Female	57.5±20.8	59.5±19.2	67.6±15.4	60.6±18.8
Total	56.3±21.1	56.5±20.2	63.3±15.1	58.0±19.2

COVID-19: Coronavirus disease-2019, SD: Standard deviation

Table 2. Distribution of patients associated with acute coronary syndrome before and during the pandemic period

	Pre-pandemic	**Pandemic**		
ACS classification	**n (%)**	**COVID-19 (–) n (%)**	**COVID-19 (+) n (%)**	**p-value**
NSTEMI	262 (48.3)	108 (39.5)	194 (76.9)	**0.001**[a]
STEMI	202 (37.3)	113 (41.4)	34 (13.6)	**0.013**[b]
USAP	78 (14.4)	52 (19.1)	24 (9.5)	0.873
Total	542 (100)	273 (100)	252 (100)	

COVID-19: Coronavirus disease-2019, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, USAP: Unstable angina pectoris ACS: Acute coronary syndrome

Pearson chi-square tests was used to compare the groups. [a]: Compared with pre-pandemic time, [b]: Compared with pre-pandemic time

in our study, the rate of ACS was observed approximately twice as high in men as in women. It was observed that NSTEMI rates increased in both genders, while STEMI rates decreased in patients presenting with ACS clinic before and during the pandemic. Similarly, NSTEMI rates were observed to be higher in both genders in patients with a diagnosis of COVID-19. In our study, when we looked at the distribution of diseases according to age ranges in patients diagnosed with cardiovascular disease, it was observed that the prevalence was higher in men between the ages of 40-69, and in women between the ages of 50-70. Although the risk increases in women after menopause, it continues to be lower than in men of the same age (29,31). In our study, when the age distribution of those with COVID-19 disease during the pandemic period was examined, an increase in the number of diseases after the age of 40 in men was observed after the age of 50 in women.

COVID-19 may have direct and indirect effects on the cardiovascular system (8-11). Patients with additional risk factors such as comorbidity associated with COVID-19, inflammatory process, cytokine storm and lung damage due to underlying comorbidity, increasing age, male gender, obesity and intensive care unit admission are at higher risk for ACS (22,23,32). It has been reported that a "cytokine storm", which is stimulated by an unbalanced response in defense cells due to infection and can cause respiratory dysfunction, hypoxemia, shock or hypotension in COVID-19 patients, causes damage to many organs, especially myocardium (33). Hypoxemia, respiratory failure, shock, and hypotension caused by pulmonary infections typically result in insufficient oxygen supply to the myocardium (34). In our study, an increase in NSTEMI rates and a decrease in STEMI rates were observed during the pandemic period. Higher rates of NSTEMI were observed in patients with COVID-19. In a study conducted in the United States, Italy and Spain, it was shown that STEMI rates decreased during the pandemic (12,35,36). Although the reasons for the decrease are unknown, a potential real decrease in acute cardiovascular events due to low stress factors during quarantine and a sedentary life are shown as the main reasons, but the thought that patients apply late for fear of catching a virus when they feel chest pain or while staying in the hospital outweighs (37). Although it is expected that the restrictions experienced in line with the measures taken during the pandemic period in our country may cause a decrease in hospital admissions, no significant difference was observed between the admission rates in our hospital. Considering the increased environmental and psychosocial stressors as a result of the

Table 3. Comparison of laboratory results in acute coronary syndrome types

ACS	Pre-pandemic		Pandemic				
		COVID-19 (-)		COVID-19 (+)			
	Mean ± SD						
	NLR	PLR	NLR	PLR	NLR	PLR	p-value
NSTEMI	2.47±1.8	110.1±48.4	2.9±2.1	109.6±64.4	3.2±2.7	125.9±82.7	**0.027**[a]
STEMI	3.49±2.5	125.8±76.4	3.4±2.5	127.7±55.6	4.1±3.2	159.8±80.7	**0.039**[b]
USAP	2.23±1.6	103.6±54.2	1.5±0.6	86.5±34.4	2.1±1.5	107.7±91.3	0.142
Total	2.91±2.5	116.5±70.4	2.7±1.6	113.3±87.1	3.8±2.4	146.4±45.3	

COVID-19: Coronavirus disease-2019, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, USAP: Unstable angina pectoris ACS: Acute coronary syndrome, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, Pearson chi-square tests was used to compare the groups [a]: compared with pre-pandemic time, [b]: compared with pre-pandemic time

Table 4. Mortality assessment before and during the pandemic

ACS cassification	Pre-pandemic	Pandemic		p-value
	n (%)	COVID-19 (-) n (%)	COVID-19 (+) n (%)	
NSTEMI	1 (25)	1 (16.6)	20 (77)	**0.001**[a]
STEMI	3 (75)	7 (87.5)	3 (11.5)	0.981
USAP	-	-	3 (11.5)	
Total	4	8	26	

COVID-19: Coronavirus disease-2019, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, USAP: Unstable angina pectoris ACS: Acute coronary syndrome,

Student's t-test and, Fisher's Exact tests were used to compare the groups [a]: compared with pre-pandemic time

effect of the pandemic, an increase in STEMI activations is expected (13). Possible etiologies for the reduction in STEMI rates include avoidance of medical care due to social distancing or concerns of contracting COVID-19 in the hospital, as well as delays in transfer times and response in emergency health services that may occur during the COVID-19 pandemic (37). It has been suggested that acute complications are facilitated as a result of the increase in NSTEMI rates in the pandemic period and in COVID-19 patients, the increase in coronary artery disease (CAD) rates due to increased systemic inflammation, acceleration of atherogenesis, and social stress (38,39). The inflammatory response with infectious agents such as COVID-19 may contribute to the acceleration of atherogenesis (39). In our results, an increase was observed in the diagnosis of CAD history when the comorbidity rates were compared before and during the pandemic. In our study, it was observed that CAD history of NSTEMI patients was higher during the pandemic and among COVID-19 patients compared to other forms. Mortality rates were higher in NSTEMI patients.

Inflammatory responses mediated by COVID-19 infection begin with adaptive immunity and neutralization of antibodies and can induce acute organ damage (40). It has been reported that myocardial damage is worsened after acute infection in patients with increased inflammatory activity, platelet activation, increased thromboxane synthesis, and impaired fibrinolytic function (32-34). Levels of biomarkers of myocardial injury are affected by many factors, including infection, hypoxia, and kidney function, so the potential for "false positives" for myocardial injury in patients with COVID-19 should be considered (41,42). More specifically, the presence or absence of myocardial injury or myocarditis should not be based solely on biomarkers of myocardial damage, but rather should be evaluated together with the results of ancillary procedures and tests after careful evaluation of all clinical parameters of the patient (43). In this context, it was found that inflammatory parameters such as CRP, NLR, PLR play a role in the monitoring of COVID-19 infection, and especially lymphocytes and platelet counts are correlated with the severity of COVID-19 disease (44). It has been stated that activation of neutrophils and changes in other leukocyte ratios during the inflammatory response in COVID-19 can be used as a prognostic indicator together with other inflammatory markers (45). Likewise, the increase in NLR observed in the early period of ACS was correlated with the mortality of acute myocardial infarction (46). CRP elevation in 80% of patients with severe COVID-19 disease who died; lympopenia was detected in 74% of them and an elevated neutrophil count was shown in 60% of them together with other inflammatory markers (47). In our study, the PLR rates of the patients were found to be higher in the pandemic period and in COVID-19 patients.

Evaluation of the study as a single-center and retrospective analysis covering a certain time period, the inability to determine the comorbidity rates of the patients clearly due to the deficiencies in the patient information system, the incompleteness of mortality information in the patients referred to an external center, the inability to follow-up the laboratory values in all patients due to the referral of some patients to an external center, can be counted among the limitations. However, our study is a strong study with a strong patient population evaluating changes in patients with ACS in one of Europe's most populous cities, where no healthcare system containment strategy against the COVID-19 pandemic has been included.

Conclusion

Cardiac complications seem to come to the fore among the acute and chronic complications of COVID-19 disease. The rapid management of ACS cases in the emergency department affects patient outcomes. Determining the severity, risk factors, laboratory findings, and outcomes of COVID-19 disease is essential to properly understand all the mechanisms that can induce ACS in SARS-CoV-2 infection, and to develop strategies to facilitate diagnosis and transfer of treatment in these patients. Thanks to the demographic characteristics, laboratory findings and patient outcomes we obtained from our study, guiding predictions can be provided in the diagnosis and treatment of critically ill patients.

The importance of the contribution of retrospective studies and case reports to the literature in the pandemic process has been seen once again. In order to guide the diagnosis and treatment guidelines, retrospective studies should continue, as well as prospective studies that will present the findings related to the relationship between coronary syndromes and COVID-19 to the literature, focused on comprehensive targets, and are suitable for clinical operation.

Ethics

Ethics Committee Approval: The study was conducted after the Declaration of Helsinki for Human Research and was approved by the local ethical review board. Ethics committee approval was obtained from the Local Non-

Interventional Clinical Research Ethics Committee of İstanbul Medipol University (E-10840098-772.02-1405, 21.03.2021).

Informed Consent: All subjects gave their informed consent for inclusion before they participated in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ç., A.C., B.D., H.K., B.A., Concept: B.Ç., A.C., B.D., B.A., Design: B.Ç., A.C., B.D., B.A., Data Collection or Processing: B.Ç., A.C., B.D., H.K., Analysis or Interpretation: B.Ç., A.C., B.A., Drafting Manuscript: B.Ç., A.C., B.D., H.K., B.A., Critical Revision of Manuscript: B.Ç., A.C., B.D., Final Approval and Accountability: B.Ç., A.C., B.D., H.K., B.A., Supervision: B.Ç., A.C., Writing: B.Ç., A.C., B.D., H.K., B.A.

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