

Evaluation of the Demographic and Laboratory Data of Patients Diagnosed with Crimean-Congo Hemorrhagic Fever in the Emergency Department and Their Relationship with Morbidity and Mortality

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Abstract

Aim: Crimean-Congo hemorrhagic fever (CCHF) is transmitted by infected ticks or through contaminated blood, tissue, and body fluids. Pathological laboratory results, such as thrombocytopenia, leukopenia, and anemia, along with biochemistry and coagulation parameters, can be used for its diagnosis and the determination of its prognosis.

Materials and Methods: Data of patients over 17 years of age diagnosed with CCHF between 2013 and 2018 were reviewed retrospectively. The complete blood count, liver-renal enzymes, electrolytes, prothrombin time, activated partial thromboplastin time (aPTT), D-dimer values, fibrinogen values, and international normalized ratio (INR) were recorded and analyzed at admission.

Results: Non-survivors had higher levels of alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase (AST), blood urea nitrogen (BUN), direct bilirubin, gamma-glutamyl transferase, creatinine, potassium, total bilirubin and uric acid ($p < 0.05$), whereas creatine kinase (CK), CK-MB, and calcium levels were lower ($p < 0.05$). Non-survivors had higher levels of basophil, mean corpuscular hemoglobin concentration, mean corpuscular volume, neutrophil, nucleated red blood cells, platelet distribution width, and white blood cells ($p < 0.05$).

Conclusion: Evaluation of routine blood parameters of CCHF patients in the emergency room is a useful tool to accelerate recovery in intensive care and prevent delay in patient treatment. Platelet, aPTT, INR, BUN, and AST values are predictors for mortality.

Keywords: Crimean-Congo hemorrhagic fever, white blood cell, thrombocyte, mortality

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is one of the most common, fatal viral hemorrhagic fevers in the world. It is seen in many countries, especially in Asia, Africa, southeast Europe, and the Middle East (1). CCHF virus causes severe and fatal infection among vertebrates only in humans (2). The cause of CCHF is an RNA virus belonging to the Nairovirus genus from the Bunyaviridae

family. The virus is transmitted to humans by infected ticks or by contact with contaminated blood, tissue, and body fluids. The risk of infection as a result of contact with infected blood is 8.7%, especially during the follow-up of patients with bleeding. The risk rises to 33% in the case of needle stick injuries. The highest transmission is observed with a percutaneous injury. The fetal transmission has been reported to a small extent (3). The disease is seen in the spring, summer, and autumn seasons and peak in July (4).



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Thrombocytopenia is a severe laboratory finding in CCHF. The presence of severe thrombocytopenia in the early period can be considered as a clue that the disease may be fatal (5). The direct cytopathic effect of the virus is blamed for liver damage in the disease. Increased liver enzymes, edema in cells, and necrosis occur as a result of the CCHF virus infecting hepatocytes widely. As a result, bleeding occurs as a result of hemophagocytosis and liver dysfunction (6-9). Thrombocytopenia, leukopenia, and neutropenia occur in almost all cases. Severe patients may have anemia. Aspartate transferase (AST), alanine transferase (ALT), lactate dehydrogenase (LDH), and creatinine phosphokinase (CPK) levels are high. Total protein and albumin values may decrease, and prothrombin time (PT) and activated partial thromboplastin time (aPTT) among hemostasis tests are prolonged. Fibrinogen levels may decrease, and fibrin degradation products may increase. In severe patients, bilirubin, urea, and creatine values may increase (10,11).

Using routine laboratory data in determining patients with fatal diseases such as CCHF will help the decision-making process of physicians. To our knowledge, there are studies on this topic in the literature, but there are limited studies with such a large number of cases. In this study, we aimed to investigate the laboratory results and demographic data of the patients who were diagnosed with CCHF in the last five years and to assess their roles in predicting mortality.

Materials and Methods

After the approval of the local ethics committee, the files of patients over the age of 17 who were diagnosed with CCHF between 2013 and 2018 were reviewed retrospectively. Ages, genders, and admission dates were recorded. The investigated admission laboratory parameters were as follows: fasting and postprandial blood glucose, alkaline phosphatase (ALP), ALT, amylase, AST, blood urea nitrogen (BUN), creatine kinase (CK), creatine kinase-MB (CK-MB), direct bilirubin, total bilirubin, gamma-glutamyltransferase (GGT), calcium (Ca), chloride (Cl), potassium (K), sodium (Na), creatinine, uric acid; basophil, eosinophil, hematocrit (HCT), hemoglobin (HGB), lymphocyte, mean corpuscular hemoglobin (MCH), mean corpuscular

hemoglobin concentration (MCHC), mean corpuscular volume (MCV), monocyte, mean platelet volume (MPV), neutrophil, nucleated red blood cells (NRBC), plasma thromboplastin component (PTC), platelet distribution width (PDW), platelets (PLT), red blood cell (RBC), white blood cell (WBC); PT, aPTT, D-dimer, fibrinogen and international normalized ratio (INR). Patients with missing data were not included in the study.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows version 23.0 (IBM, Armonk, NY, USA), and continuous data were reported as mean \pm standard deviation or median, and categorical data were given as number and percentage. Kolmogorov-Smirnov test was used as a test for normality for continuous data, and parametric paired and unpaired t-tests were used. Receiver operating characteristic (ROC) analysis was used to determine the diagnostic efficiency of the laboratory parameters.

Results

Table 1 presents the gender distribution of patients with CCHF according to mortality. No statistically significant difference was observed between the two groups in terms of gender ($p>0.05$). No statistically significant difference was observed in the within-group evaluations. There was no effect of gender on mortality in CCHF patients. When the age was compared in terms of mortality, no statistically significant difference was found between the groups.

The distribution of patients according to the months of admission is given in Figure 1. The highest admission total was recorded as 134 patients in July. Again, the highest mortality was observed in July. No statistically significant difference was found in comparing the mortality of the disease by months ($p>0.05$).

Table 2 shows the comparison of the laboratory data of the survivors and non-survivors. Regarding biochemistry parameters, non-survivors had higher levels of ALP, ALT, Amylase, AST, BUN, direct bilirubin, GGT, creatinine, K, total bilirubin and uric acid levels and this was statistically significant ($p<0.05$). In the non-

Gender	Non-survivors (%)	Survivors (%)	p
Female	11 (36.7%)	191 (41.3%)	>0.05
Male	19 (63.3%)	271 (58.7%)	
	p>0.05	p>0.05	
Age	59.76 \pm 15.89	53.54 \pm 15.89	>0.05

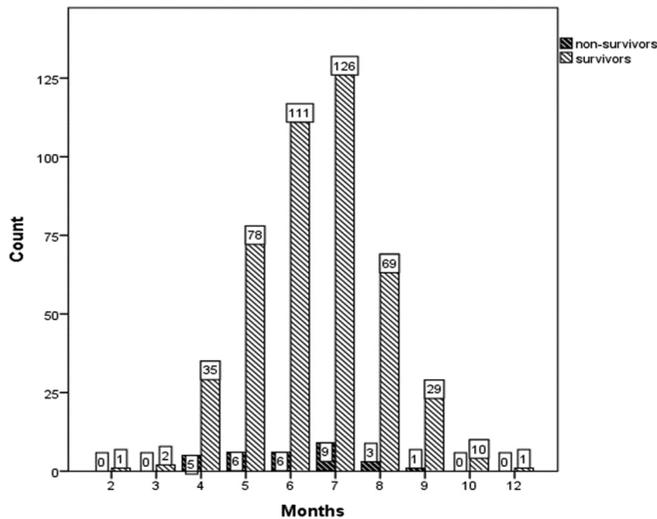


Figure 1. The distribution of patients according to the months of admission

survivor group, CK, CK-MB, and Ca levels were lower, and this was statistically significant ($p < 0.05$). No statistically significant difference was found in fasting and postprandial glucose levels, Na and Cl levels between two groups ($p > 0.05$). Regarding complete blood count (CBC) parameters, non-survivors had higher levels of basophil, MCHC, MCV, neutrophil, NRBC, PDW, and WBC, and this was statistically significant ($p < 0.05$). There was no statistically significant difference in terms of HCT, HGB, MCH, MPV, PDW, RBC, eosinophil, and lymphocyte count between two groups ($p > 0.05$). In the non-survivor group, monocyte, PTC, and PLT levels were lower, and this was statistically significant ($p < 0.05$). Regarding coagulation parameters, non-survivors had higher levels of aPTT, D-dimer, and INR, and this was statistically significant ($p < 0.05$). In the non-survivor group, fibrinogen and PT levels were lower, and this was statistically significant ($p < 0.05$).

Table 3 shows the sensitivity, specificity, positive predictive values, negative predictive values, and area under curve values of the laboratory values of the patients according to the ROC analysis. AST and BUN from biochemical parameters, PLT from CBC parameters, and aPTT and INR from coagulation parameters had the highest AUC parameters. Figure 2 shows the ROC analysis charts.

Discussion

Our study, in which we examined a large number of patient populations, revealed that ALT, AST, BUN, creatinine, CK-MB, aPTT, INR, PT, fibrinogen, and PLT could be functional determinants in demonstrating CCHF mortality.

In the studies conducted, no statistically significant difference was found between the survivors and non-survivors in terms of age and gender (12-14). In our study, in accordance with the literature, both groups show similar characteristics in terms of age and gender. Again, in our study, it was observed that the mortality was high in June and July when the disease was prevalent.

When the literature is reviewed, CBC parameters were evaluated in many studies. In a study of 152 patients with CCHF evaluated by Yilmaz et al. (15), admission HGB and PLT values were lower in the severe patient group than in the non-severe group, and this difference was significant (HGB cut-off: 13.5, AUC: 0.61, PLT cut-off: 90,000, AUC: 0.70). They stated that WBC was similar in both groups, and there was no statistical difference. In a study by Hatipoglu et al. (14), they examined the laboratory data of 152 CCHF patients as predictors of mortality. They found that HGB and WBC values were high in patients with mortality, and PLT values were low. In a study conducted by Arslan et al. (16), PLT and HGB values were found to be significantly lower in patients with bleeding compared to the group with no bleeding, and they did not find a statistically significant difference between WBC and CRP values. In the study by Öngörü et al. (12) in which they examined the relationship between coagulation parameters and mortality in CCHF patients, they found that PLT rates were significantly lower in the non-survivors. In the study of evaluating the laboratory and clinical features of CCHF patients as predictors of mortality, Kazancıoğlu et al. (17) evaluated a total of 92 patients (77 survivors and 15 non-survivors). They found that the admission levels of HB and WBC did not differ significantly between the non-survivors and survivors. The admission PLT levels were found to be statistically significantly lower in the non-survivors. They found a cut-off value of $< 30,000$ for admission PLT with 85.7% sensitivity and 81.8% specificity (AUC: 0.840). In the severity scoring system of CCHF developed by Bakır et al. (18), PLT decrease and WBC increase are included in the scoring system. In our study, we found many significant differences in CBC parameters, but according to ROC analysis, the PLT cut-off value of $< 119,500$ was the most successful parameter with 79% sensitivity and 83% specificity. These values were also compatible with the literature. Studies reported different opinions with WBC increase. In our study, WBC was significantly higher in the non-survivor group. Again, there are conflicting opinions about HB in the literature. In our study, we found that admission HGB level was not significantly different between the two groups. We think that additional attention should be paid to the lower HGB levels in patients presenting with bleeding.

Table 2. Comparison of laboratory data between survivors and non-survivors diagnosed with CCHF

Laboratory parameters (25-75%)	Non-survivors (n=30)	Survivors (n=462)	p
HCT (%)	44.95 (41.6-51.1)	43.65 (40.3-46.9)	0.068
HGB (g/dL)	15.2 (14.4-17.4)	14.7 (13.5-16)	0.073
Lymphocytes (%)	32 (21.8-47.4)	46.9 (34.4-56)	0.001
MCH (g/dL)	30.65 (29.1-31.5)	29.90 (28.7-31.1)	0.091
MCHC (g/dL)	34.95 (34.4-36.4)	34.60 (33.7-35.3)	0.028
MCV (%)	89.75 (86.5-92.4)	87.90 (84.4-91.4)	0.045
Monocytes (%)	5.05 (2.3-9.3)	12.03 (9-15.6)	0.001
MPV (%)	11.45 (10.7-12.4)	11.05 (10.2-12)	0.127
Neutrophils (%)	84.25 (77.6-89.1)	71.6 (58.8-84.3)	0.001
PTC (%)	0.09 (0.05-0.11)	0.16 (0.12-0.2)	0.001
PDW (%)	17.05 (15.80-18.70)	16.60 (15-19.10)	0.014
PLT (1,000/uL)	81 (40-115)	156 (125-206)	0.001
RBC (10 ⁶ /uL)	5.2 (4.7-5.92)	5.08 (4.68-5.47)	0.201
WBC (μL)	8.11 (4.04-15.74)	5.53 (4.26-7.56)	0.004
Fasting glucose (mg/dL)	160.5 (107-205)	111 (97-135)	0.065
ALP (U/L)	226 (153-279)	87 (67-125)	0.001
ALT (U/L)	728 (235-1782)	94.5 (39-181)	0.001
Amylase (U/L)	159 (109-300)	76 (57-110)	0.001
AST (U/L)	2,397 (626-8,377)	128.5 (48-311)	0.001
BUN (mg/dL)	49.78 (34.09-79.73)	16.72 (12.24-22.98)	0.001
CK (U/L)	1417.5 (677.5-818)	232 (112-699)	0.001
CK-MB (U/L)	78 (44-134)	28.8 (21-43)	0.001
Direct bilirubin (U/L)	1.67 (0.07-10.84)	0.19 (0.12-0.35)	0.001
GGT (U/L)	213.5 (119-363.5)	57 (25-150)	0.001
Ca (mg/dL)	7.7 (7.47-8.97)	8.76 (8.34-9.12)	0.001
Cl (mEq/L)	106 (103-110)	105 (102-107)	0.078
Creatinine (mg/dL)	3.05 (1.71-4.74)	0.89 (0.75-1.09)	0.001
K (mEq)	4.94 (4.22-5.53)	4.35 (3.98-4.76)	0.001
Na (mEq/L)	140 (136-145)	139 (136-141)	0.203
Total bilirubin (U/L)	2.78 (0.83-4.81)	0.54 (0.4-0.94)	0.001
Uric acid (mg/dL)	7.7 (6.1-10.4)	4.80 (3.6-6.1)	0.001
aPTT (sec)	65.2 (53.9-75.7)	34.6 (30.5-41.2)	0.001
D-Dimer (μg/mL)	24,110 (5,780-6,895)	713 (179-2,692)	0.001
Fibrinogen (mg/dL)	224 (195-257)	345 (292-428)	0.001
INR	1.79 (1.42-2.64)	1.11 (1-1.28)	0.001
PT (sec)	20.9 (16.4-28.8)	13.25 (11.8-14.9)	0.001

CCHF: Crimean-Congo hemorrhagic fever, HCT: Hematocrit, HGB: Hemoglobin, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, MPV: Mean platelet volume, PTC: Plasma thromboplastin component, PDW: Platelet distribution width, PLT: Platelets, RBC: Red blood cell, WBC: White blood cell, ALP: Alkaline phosphatase, ALT: alanine transferase, AST: Aspartate transferase, BUN: Blood urea nitrogen, CK: Creatine kinase, CK-MB: Creatine kinase-MB, GGT: Gamma-glutamyltransferase, Ca: Calcium, Cl: chloride, K: Potassium, Na: Sodium, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: prothrombin time, n: Number
Important values are shown in bold

Table 3. Sensitivity, specificity, positive predictive values, negative predictive values and area under curve values of the patients' laboratory values according to ROC analysis

Test result variable(s)	AUC	SE	Asymptotic 95% confidence interval					p	PPV	NPV
			Lower bound	Upper bound	Cut-off	Sensitivity	Specificity			
ALP	0.849	±0.039	0.773	0.925	144	0.833	0.765	0.000	79.3	80.9
ALT	0.863	0.049	0.767	0.958	216	0.833	0.752	0.000	79.3	79.5
Amylase	0.807	0.057	0.695	0.918	124.5	0.778	0.797	0.000	74.1	79.8
AST	0.911	0.032	0.848	0.974	620.5	0.833	0.865	0.000	79.2	88.3
BUN	0.919	0.021	0.879	0.959	26.20	0.944	0.778	0.000	89.7	81.5
CK	0.811	0.040	0.733	0.889	524.5	0.889	0.691	0.000	83.3	70
CK-MB	0.873	0.036	0.803	0.944	43.95	0.889	0.752	0.000	80	75.9
GGT	0.754	0.056	0.644	0.864	178	0.722	0.778	0.000	60.7	80.1
Creatinine	0.910	0.032	0.848	0.972	2.015	0.833	0.910	0.000	72.4	92.8
Uric acid	0.840	0.039	0.764	0.917	6.050	0.833	0.733	0.000	81	74.9
aPTT	0.932	0.025	0.883	0.981	48.7	0.893	0.882	0.000	86.2	88.3
D-dimer	0.816	0.052	0.715	0.918	5174.5	0.786	0.848	0.000	78.6	84.3
INR	0.886	0.035	0.818	0.954	1.4150	0.750	0.862	0.000	75.9	86.5
PT	0.878	0.037	0.806	0.950	16.350	0.750	0.857	0.000	75.9	86
Fibrinogen*	0.831	0.054	0.726	0.936	257.50	0.904	0.759	0.000	75.9	90.1
Calcium*	0.722	0.062	0.600	0.843	8.1850	0.828	0.621	0.000	62	83
PLT*	0.865	0.04	0.774	0.955	119.50	0.790	0.833	0.000	83.3	79.4

ROC: Receiver operating characteristic curve, AUC: Area under the curve, SE: Standard error, PPV: Positive predictive value, NPV: Negative predictive value, ALP: Alkaline phosphatase, ALT: alanine transferase, AST: Aspartate transferase, BUN: Blood urea nitrogen, CK: Creatine kinase, CK-MB: Creatine kinase-MB, GGT: Gamma-glutamyltransferase, ^aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: prothrombin time, PLT: Platelets
*: Increasing in fibrinogen and platelets and decrease of the other values were calculated

There are many studies examining biochemical parameters in CCHF. In these studies, especially AST, ALT, ALP, LDH values were found to be higher in severe patients (12-14,16). In the study conducted by Yilmaz et al. (15), no statistically significant difference was found between BUN and creatinine levels between clinically severe and mild groups. In the study of Kazancıoğlu et al. (17), admission urea and creatinine levels were found to be significantly higher in the non-survivor group. The sensitivity and specificity of urea for a cut-off value of 27.5 were 92.9% and 58.4%, respectively (AUC=0.760). Similar to these studies, in our study, AST, ALT, ALP, LDH, GGT, CK, CK-MB, BUN, creatinine, and uric acid were higher in the non-survivor group, and these were statistically different parameters. Especially BUN and AST were the biochemical parameters to be considered in the non-survivor group. BUN cut-off value of 26.2 had 94.4% sensitivity and 77.8% specificity. AST cut-off value of 620 had 83% sensitivity and 86% specificity. In another study, Ca levels in children with CCHF were found to be low (18). We also found that Ca levels were significantly lower in the non-survivor group.

Abnormal bleeding time and coagulation parameters can be counted as the most common laboratory findings in patients with CCHF. When we look at the studies in the literature, an increase in aPTT, PT, PTT, and INR, and a decrease in fibrinogen are observed (19-21). In our study, we also found PT, aPTT, INR, and D-dimer increase and fibrinogen decrease in accordance with the literature. Especially aPTT and INR elevation had the highest sensitivity and specificity among these parameters. The aPTT cut-off value of 48.7 had 89.3% sensitivity and 88.2% specificity. INR cut-off value of 1.41 had 75% sensitivity and 86% specificity.

Conclusion

Evaluation of routine blood parameters of CCHF patients in the emergency room is a useful tool to accelerate hospitalization in intensive care and to prevent delay in the treatment of the patient. It should be kept in mind that PLT, aPTT, INR, BUN, and AST values, especially in patients with suspected CCHF, are predictors of mortality.

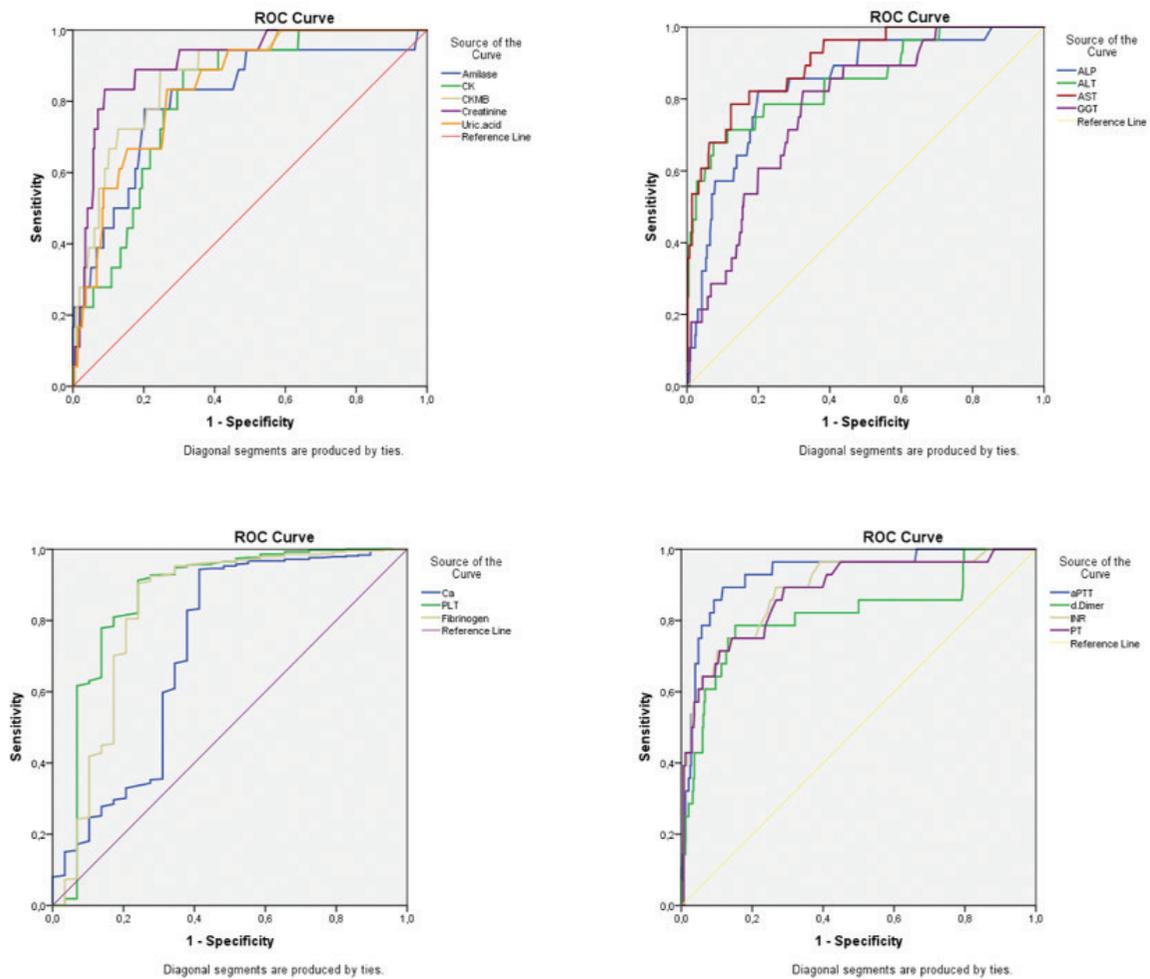


Figure 2. Shows the ROC analysis charts

ROC: Receiver operating characteristic curve, CK: Creatine kinase, CK-MB: Creatine kinase-MB, ALP: Alkaline phosphatase, ALT: Alanine transferase, AST: Aspartate transferase, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time, PLT: Platelets

Ethics

Ethics Committee Approval: This retrospective study was approved by the institutional human ethics committee [Sivas Cumhuriyet University Ethics Committee (2018-11/06)].

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ü.S., E.D., S.A.B., Y.K.T., Concept: E.D., Y.K.T., Design: E.D., S.A.B., Y.K.T., Data Collection or Processing: İ.K., Y.K.T., S.Y., Analysis or Interpretation: E.D., İ.K., S.Y., Literature Search: E.D., S.A.B., S.Y., Writing: E.D., İ.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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