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Factors related to mortality in hemodialysis patients with COVID-19

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ABSTRACT

Introduction: The mortality rate in COVID-19 patients is about 2%, however advanced age, male gender, comorbid diseases increase the risk of mortality. Patients with end-stage renal disease (ESRD) and hemodialysis (HD) treatment are more susceptible to infection due to both existing comorbid diseases and immune suppression caused by uremia.

Objectives: This study aims to show the potential of easily obtainable, inexpensive and reproducible markers in predicting mortality in HD patients at the time of diagnosis.

Patients and Methods: In this study, we examined the relationship between; neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV) and C-reactive protein (CRP)/albumin values at the time of hospital admission with mortality in 75 HD patients diagnosed with COVID-19. All analyses were conducted using IBM SPSS Statistics 21.0 and MS-Excel 2010 software.

Results: A total of 75 HD patients diagnosed with COVID-19 were included in the study. Out of these, at least 19 (25.3%) patients received hydroxychloroquine, 68 (90.6%) patients favipiravir, two (2.6%) patients tocilizumab and two patients (2.6%) immune plasma therapy. Among these patients, sixteen patients (21.3%) needed invasive mechanic ventilation, eight patients (10.6%) needed high flow oxygen and seven patients (9.3%) needed non-invasive mechanic ventilation and 17 of 75 patients (23%) died. A total of 14 of the 17 non-survivors were intubated. In comparison between survivors and non-survivors in our study; NLR, MPV, CRP, CRP/albumin and phosphorus values were significantly higher in the non-survivors group.

Conclusion: According to this study, NLR, MPV and CRP/albumin values are associated with mortality in HD patients affected with COVID-19.

Original

Implication for health policy/practice/research/medical education:
COVID-19 positive hemodialysis patients have increased mortality risk. This study aims to show the potential of easily obtainable, inexpensive and reproducible markers in predicting mortality in hemodialysis patients at the time of diagnosis. In this study, NLR, MPV and CRP/albumin values are associated with mortality in HD patients affected with COVID-19.

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Introduction

The COVID-19 outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which emerged in Wuhan, China's Hubei province on December 31, 2019, quickly spread to six continents and hundreds of countries and went down in history as the first pandemic caused by coronaviruses (1,2). The COVID-19 pandemic continues to be a serious public health problem all over the world. The epidemic process in Turkey started with the diagnosis of the first case on March 11, 2020. Since the isolation of the novel coronavirus, studies on COVID-19 disease and SARS-CoV-2 virus have been initiated in many countries. COVID-19 infection shows a highly variable course from an asymptomatic or oligosymptomatic to severe organ dysfunction and death. Commonly, clinical symptoms such as fever, non-productive cough, shortness of breath, myalgia, general fatigue, sore throat and headache are observed. Severe lung failure (acute respiratory distress syndrome, ARDS), heart and kidney failure may occur (3,4). The mortality rate is about 2%, advanced age, male gender, comorbidities such as hypertension and diabetes

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increases the risk of mortality (5-7). Patients with end-stage renal disease (ESRD) and undergoing hemodialysis (HD) treatment are more susceptible to infection due to both existing comorbid diseases and immune suppression caused by uraemia. For this reason, infections are among the leading causes of death in HD patients all over the world (8). Few studies have shown that COVID-19 has high mortality in HD patients (9-11). Identifying the causes that increase mortality may help in reducing it through additional measures and early interventions while treating the patients. In this study, we examined the relationship between neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV) and C-reactive protein (CRP)/albumin values at the time of hospital admission with mortality in 75 HD patients diagnosed with COVID-19.

Objectives

This study aims to show the potential of easily obtainable, inexpensive and tests of markers in predicting mortality in HD patients at the time of diagnosis.

Patients and Methods

Seventy-five HD patients with the report of lung computerised tomography (CT) that is compatible with COVID-19 and/or positive COVID-19 polymerase chain reaction (PCR) matching the COVID-19 probable case definition were included in the study. According to Turkish guidelines for COVID-19 CT is an early, sensitive diagnostic approach in PCR negative yet strongly suspected patients (12). Computerised tomography imaging findings are as follows; (i) peripheral, bilateral (multilobar) ground-glass opacities (with/without consolidation), (ii) multifocal rounded ground-glass opacity, (iii) reverse halo sign or organised pneumonia were typical and frequently reported about COVID-19 pneumonia. Patients with CT findings that are compatible with COVID-19 were considered positive although the PCR results were negative.

Study design

The study has been designed as a retrospective cross-sectional study. The demographic characteristics (such as age, gender and dialysis duration) of the patients included in the study, chronic diseases, complaints at the time of admission, pH, oxygen saturation (SO_2), lactate (mmol/L), bicarbonate (HCO_3), white blood cell count (WBC, 10^6/L), neutrophil count (10^6/L), lymphocyte count (10^6/L), platelet count (10^6/L), hemoglobin (g/dL), MPV (fL), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), total bilirubin (mg/dL), lactate dehydrogenases (LDH, U/L), creatinine kinase (CK, U/L), blood urea nitrogen (BUN, mg/dL), creatinine (mg/dL), albumin (mg/dL), D-dimer (ng /mL), biomarker values such as ferritin (ng/mL), CRP (mg/L) and procalcitonin (PCT, ng/mL). The details about admission to the ICU during follow-up, the treatments received and survival was recorded from patient files and electronic data retrospectively. Only the laboratory values of the patients at the time of admission were included in the study. The neutrophil-lymphocyte ratio (NLR) was obtained by dividing the number of neutrophils by the number of lymphocytes, the platelet lymphocyte ratio (PLR) is calculated by dividing the platelet number by the number of lymphocytes and the CRP/albumin ratio by dividing the CRP value by the albumin value. CT scan images and reports of the patients were accessed from the hospital's information system.

Statistical analysis

All analyses were conducted using the IBM SPSS Statistics 21.0 and MS-Excel 2010 software. Results are presented as median (interquartile range). Pearson's chi-square and Fisher's exact test were employed for categorical variables, where appropriate. Receiver operating characteristics (ROC) analysis was performed to assess the best cut-off value for predicting mortality. We also performed a univariate logistic regression (Cox and Snell R^2) for mortality (dependent), establishing predicting factors such as NLR, CRP/albumin, MPV and phosphorus (independent variables) and their odds ratios (OR). The Hosmer-Lemeshow test was conducted as a goodness of fit test. Two-side *P* values <0.05 were considered statistically significant. Bonferroni correction was applied as post-hoc after the Kruskal-Wallis H test.

Results

A total of 75 HD patients diagnosed with COVID-19 were included in the study. The mean age of the patients was 60.7 ± 13.5 (min: 31, max: 87), 54.7% (n = 41) were female, 45.3% (n = 34) were male. The most common comorbid diseases in patients were determined as hypertension, diabetes and coronary heart disease. The demographic data and laboratory values of the patients are presented in Table 1.

All patients were treated in line with the guidelines set by our ministry of health. A total of 19 patients (25.3%) received hydroxychloroquine, 68 patients (90.6%) received favipiravir, two patients (2.6%) tocilizumab and two patients (2.6%) received immune plasma therapy. All of the non-survivors received favipiravir treatment. Low-molecular weight heparin was administered to 60 (80%) patients, high dose vitamin C to 4 (5.3%) patients, a steroid to 44 (58.6%) patients and antibiotics to 68 (90.6%) patients. Sixteen patients (21.3%) needed invasive mechanical ventilation, 8 patients (10.6%) needed high flow oxygen and seven (9.3%) patients needed non-invasive mechanical ventilation. A total of 14 of the 17 non-survivors were intubated. Only two patients who were intubated recovered. Since the aim of our study was to examine the relationship between simple parameters at the time of diagnosis and mortality, the relationship

Table 1. Demographic and laboratory characteristics of the patients

Characteristics	
Age	60.7 ± 13.5 (31-87)
Gender (F/M)	41/34 (54.6%)
Dialysis duration (month)	58.8 ± 39.9 (2-237)
PCR +/-	62/13 (82.7%)
CT +/-	64/7 (85.3%)
Comorbid diseases	
Hypertension	71/4 (94.6%)
Diabetes mellitus	38/37 (50.6%)
Coronary heart disease	55/20 (73.3%)
Heart failure	16/59 (21.3%)
COPD	15/60 (20%)
Malignancy	3/72 (4%)
Symptoms	
Shortness of breath	48/27 (64%)
Cough	51/24 (68%)
Myalgia	55/20 (73.3%)
Fever	32/43 (42.6%)
Diarrhoea	9/66 (12%)
WBC (10^6/L)	6.377 ± 3.557 (1.890-21.970)
Neutrophil (10^6/L)	4.803 ± 3.404 (1.280-20.060)
Lymphocyte (10^6/L)	920 ± 549 (80-3.570)
NLR	6.9 ± 6.1 (0.86-31.34)
Hemoglobin (gr/dL)	11.2 ± 2.2 (7.1-16.5)
Platelet (10^6/L)	171.881 ± 56.869 (58.000-323.000)
PLR	250.7 ± 294.7 (45.94-1425)
MPV (fL)	11.1 ± 1.1 (8.5-13.7)
T. Bilirubin	0.55 ± 0.5 (0.2-2.8)
AST (U/L)	46.7 ± 70.8 (7-461)
LDH (U/L)	402.1± 331.7 (127-2472)
CK (U/L)	221.6 ± 344.6 (18-2064)
Albumin (g/L)	35.1 ± 5 (21-43)
Total Protein (g/L)	61.4 ± 7.4 (46-80)
Calcium (mg/dL)	8.8 ± 0.8 (7.1-11.4)
Phosphorus (mg/dL)	5.4 ± 2.2 (2.2-12.5)
Uric acid (mg/dL)	5.5 ± 1.8 (2.3-12)
Ferritin (ng/mL)	1454.8 ± 1392.6 (158.8-8251.8)
D-dimer (ng/mL)	4.7 ± 7.3 (0.35-34.87)
INR	1.4 ± 0.9 (0.88-6.74)
CRP (mg/L)	85.2 ± 81.6 (2.69-343)
CRP/albumin	2.6 ± 2.6 (0.8-11.03)
Procalcitonin (ng/mL)	8.9 ± 22.7 (0.24-0.98)
SO_2 (%)	89.1 ± 7.8 (65-98)
pH	7.3 ± 0.1 (7.05-7.53)
Lactate (mmol/L)	2.5 ± 2.6 (0.7-1.7)

PCR, polymerase chain reaction; CT, computerised tomography; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MPV, mean platelet volume; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; INR, international normalised ratio; CRP, C-reactive protein; SO_2, oxygen saturation.

between the treatments given to patients and mortality was not evaluated.

This study showed, no significant difference was observed in terms of gender, dialysis duration, PCR positivity and CT findings among survivors and non-survivors. While it was observed that the complaint of shortness of breath at the time of admission was significantly higher among non-survivors ($P<0.001$). In the comparison of comorbid diseases, heart failure and coronary heart disease were found more frequent in non-survivors ($P<0.031$, $P<0.006$ respectively). When laboratory values were compared, a statistically significant difference was observed in almost every parameter between both groups. Findings are presented in Table 2.

Finally, logistic regression analyses were performed to identify the association of various factors with $P<0.05$ such as SO_2 < 90%, NLR ≥ 7.35, CRP/albumin ≥ 2.28, MPV ≥ 11.25 fl, phosphorus ≥ 5.5 mg/dL with the risk of mortality (Table 3). ROC analysis was conducted to determine the best cut-off value for all continuous variables producing significant results in univariate analysis. ORs and significance levels of univariate analysis were shown in Table 4.

Discussion

Approximately 80% of patients with SARS-CoV-2 infection are asymptomatic, while 20% may develop severe pneumonia. At least 25% of patients can be lost due to respiratory failure, thrombosis or multi-organ failure (12). Although mortality rates for this infection may vary (13,14) with advanced age, the presence of comorbid diseases such as hypertension, cardiovascular disease, severe dyspnoea, lymphopenia and increased LDH are associated with mortality (15). In a retrospective study conducted by the Chinese Centre for Disease Prevention and Control among 44,672 patients with COVID-19, the mortality rate in patients with cardiovascular disease, diabetes, chronic lung disease and hypertension was 10.5%, 7.3%, 6.3% and 6% respectively (16). In another study, 63% of those with severe COVID-19 were found to have hypertension (17). Most of the HD patients have these comorbid diseases, which are risk factors for COVID-19. These patients are at risk for COVID-19 because of both uremia-induced immunosuppression and these comorbid diseases (18,19). Studies conducted with HD patients have demonstrated a higher mortality rate than the normal population (20-24). The most common symptoms of patients were cough, shortness of breath and myalgia in our study. Tortonese et al, in their study of 44 HD patients, found that the most common symptoms are fever and cough (25). In another study by Fisher et al, the most common symptom was shortness of breath, while fever was found in the second-order (26). In our study, fever was found in 41% of the patients. In our study also 94.7% of 75 patients had hypertension, 73.3% had coronary heart disease and 50.7% had diabetes. Coronary

Table 2. Comparison of survivors and non-survivors

	Non-survivors (n = 17)	Survivors (n = 58)	*P* value
Age	70.1 ± 11.3	57.8 ± 12.9	0.003[a]
Gender (F/M)	6/11	35/23	0.068
Dialysis duration (month)	63 ± 30.8	57.5 ± 42.4	0.401
PCR +/-	14/3	48/10	NA
CT +/-	17/0	47/7	0.174
Comorbid diseases			
Hypertension	16/1	55/3	NA
Diabetes mellitus	12/5	26/32	0.062
Coronary heart diseases	16/1	39/19	0.031[a]
Heart failure	8/9	8/50	0.006[a]
Chronic obstructive pulmonary disease	3/14	12/46	NA
Symptoms			
Shortness of breath	17/0	31/27	<0.001[a]
Cough	10/7	41/17	0.356
Myalgia	15/2	40/18	0.134
Fever	5/12	27/31	0.209
Laboratory			
WBC (10^6/L)	9.627 ± 4.698	5.366 ± 2.398	<0.001[a]
Neutrophil (10^6/L)	8.431 ± 4.379	3.674 ± 2.028	<0.001[a]
Lymphocyte (10^6/L)	739 ± 269	976 ± 602	0.173
NLR	12.6 ± 7.1	5.2 ± 4.5	<0.001[a]
Haemoglobin (g/dL)	12 ± 2.5	10.9 ± 2.1	0.222
Platelet (10^6/L)	172.786 ± 56.192	171.600 ± 57.705	0.817
PLR	269.5 ± 177.4	244.9 ± 214	0.383
MPV (fL)	11.9 ± 0.9	10.8 ± 1.1	0.001[a]
T. Bilirubin	0.95 ± 0.8	0.42 ± 0.2	0.004[a]
AST (U/L)	105.2 ± 122.3	28,1 ± 25,7	<0.001[a]
LDH (U/L)	687.8 ± 557.2	309 ± 120.5	<0.001[a]
CK (U/L)	465.6 ± 533.9	142.2 ± 209.2	0.009[a]
Albumin (g/L)	31.7 ± 4.6	36.2 ± 4.7	0.002[a]
Total protein (g/L)	56.1 ± 7.4	63.2 ± 6.7	0.004[a]
Calcium (mg/dL)	8.7 ± 0.9	8.8 ± 0.8	0.703
Phosphorus (mg/dL)	6.8 ± 2.7	4.9 ± 1.8	0.009[a]
Uric acid (mg/dL)	6.5 ± 2.2	5.2 ± 1.6	0.024[a]
Ferritin (ng/mL)	2.3524 ± 2.2061	1.1057 ± 678.2	0.012[a]
D-dimer (ng/mL)	9.9 ± 11,9	2.6 ± 2.3	0.057
INR	1.89 ± 1.61	1.12 ± 0.19	0.026[a]
CRP (mg/L)	141.6 ± 92.6	66.9 ± 69.3	0.004[a]
CRP/albumin	4.45 ± 2.91	1.99 ± 2.22	0.001[a]
Procalcitonin (ng/mL)	17.9 ± 32.8	3.6 ± 11.9	0.001
SO_2 (%)	80.6 ± 8.8	91.8 ± 5.2	<0.001[a]
pH	7.29 ± 0.13	7.35 ± 0.1	0.194
Lactate (mmol/L)	3.9 ± 4.1	1.7 ± 0.7	0.003[a]

PCR, polymerase chain reaction; CT, computerised tomography; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MPV, mean platelet volume; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; INR, international normalised ratio; CRP, C-reactive protein; SO_2, oxygen saturation.

Mann Whitney U test was used for non-parametric numerical variables, Pearson's chi-square and Fischer's exact tests were used for categorical variables.

[a] Significant.

heart disease and heart failure were more common in the non-survivor expected. Cardiac issues are the most common cause of death in HD patients. The mortality rate in our study was 23% higher than studies conducted in the general population. The mean age (70.1 ± 11.3 years) of non-survivors was found to be significantly higher. All these findings are consistent with the literature.

Decreased lymphocyte, haemoglobin and platelet count and a significant increase in the neutrophil count were detected in severe COVID-19 patients. Results in studies conducted with HD patients are contradictory. In a multicentre study by Xiong et al investigating 154 patients, no significant difference was found between WBC, neutrophil and lymphocyte counts between patients with and without the serious disease (10). In a study conducted by Shang et al, WBC and neutrophil counts of 9 HD

Table 3. Receiver operating characteristic (ROC) curve analysis to distinguish mortality

Parameters	AUROC	95% CI		Cut-off value	Sensitivity	Specificity	*P* value
		Lower	Upper				
Age (years)	0.763	0.624	0.902	63	78.7%	65.2%	0.003
SO_2 (%)*	0.887	0.787	0.988	89	78.6%	80.0%	<0.001
NLR	0.863	0.754	0.973	7.35	85.7%	82.0%	<0.001
CRP/albumin (10^{-3})	0.799	0.667	0.931	2.28	78.6%	71.4%	0.001
MPV (fL)	0.785	0.655	0.915	11.25	78.6%	71.1%	0.001
Phosphor (mg/dL)	0.734	0.582	0.887	5.5	71.4%	67.5%	0.009

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; MPV, mean platelet volume.
Note: Unlike the others, the test direction in the analysis for SO2 is set to "the smaller test result indicates the more positive test".

Table 4. Evaluation of factors associated with mortality by univariate logistic regression analysis

Parameters	R^2	βi	Odds ratio	95% CI		Wald value	*P* value
				Lower	Upper		
Age ≥ 63 years	0.13	1.93	6.88	1.67	28.27	7.15	0.008[a]
SO_2 ≤ 89%	0.24	2.68	14.67	3.37	63.84	12.81	<0.001[a]
NLR ≥ 7.35	0.31	3.32	27.75	5.17	149.00	15.02	<0.001[a]
CRP/albumin ≥2.28 (10^{-3})	0.18	2.22	9.17	2.17	38.75	9.08	0.003[a]
MPV ≥ 11.25 fL	0.18	2.25	9.47	2.24	39.98	9.36	0.002[a]
Phosphorous ≥ 5.5 mg/dl	0.01	1.54	4.67	1.30	17.44	5.25	0.022[a]

βi, Regression coefficient; CI, confidence interval; SO_2, oxygen saturation; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; MPV, mean platelet volume.
Univariate logistic regression analysis was used. Cox & Snell R^2 was preferred.
[a] Significant.

patients who died were found to be significantly higher, while no difference was found between lymphocyte counts (27). Zhang et al compared the haematological parameters of 31 HD patients during infection with their values three months ago. They observed a significant decrease in lymphocyte count, while a non-significant decrease in WBC and neutrophil values was observed (28). We found a significant increase in WBC and neutrophil values and a significant decrease in lymphocyte values in our patients at the time of admission.

In another study showed that LDH and CRP levels may be an early indicator of the risk of developing ARDS (29). Bonetti et al found significantly higher levels of AST, D-dimer, CRP, CK and LDH, in 70 patients who died (30). In studies conducted with HD patients, it has been shown that AST, LDH, CRP, ferritin and D-dimer values are significantly higher in patients with severe disease and non-survivors. Results vary for PCT and creatine kinase (7,26,27,31). In our study; while AST, LDH, CK, ferritin, D-dimer, total bilirubin and CRP were significantly higher in the non-survivor group, albumin and total protein were significantly lower. There was not a significant difference for the PCT. The neutrophil-lymphocyte ratio is an important parameter that can be easily calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and indicating the inflammation. Increased NLR is highly associated with mortality not only in infectious diseases but also in conditions such as malignancy, acute coronary syndrome and intracerebral haemorrhage (32–34). Liu et al showed that the NLR value is an independent risk factor for mortality in hospitalised patients (35). Zhang et al also showed that severe cases of COVID-19 have a higher NLR (36). MPV is associated with thrombosis, inflammation and cardiovascular events and higher MPV values are found in patients with myocardial infarction (MI) (37,38). The clinical significance and the effects of NLR, MPV, PLR and CRP/albumin values on HD patients with COVID-19 infection have not yet been demonstrated. In the comparison of survivors and non-survivors in our study; NLR, MPV, CRP, CRP/albumin and phosphorus values were found to be significantly higher in the non-survivor group. The significant effects of these parameters on mortality were shown in the ROC analysis. The sensitivity and specificity of NLR in predicting mortality was 85.7% and 82.0% respectively. The sensitivity of the CRP/albumin was 78.6%, the specificity was 71.4%, the sensitivity of the MPV was 78.6%, and the specificity was 71.1%. As a result of univariate regression analysis, mortality was found to be significantly higher in patients with NLR ≥7.35, CRP/albumin ≥2.28, MPV ≥11.25 fl and phosphorus ≥ 5.5 mg/dL.

Maintaining normal serum phosphorus is very important for HD patients. Dietary restrictions, phosphate-binding medications and effective dialysis are required for normal serum levels. Therefore, serum phosphorus levels are an

indicator of dialysis efficiency. Both very high and very low-phosphorus values are independently associated with an increased risk for all-cause mortality in HD patients (39). In our study, it was shown that high serum phosphorus levels increase mortality, while stable serum phosphorus levels can improve survival in HD patients. A previous study also addressed this finding (40). In the study conducted by Yang et al, a positive correlation was found between hypophosphatemia and the severity of COVID-19 (41). In our study, high phosphorus values detected at the time of diagnosis of COVID-19 were found to be associated with mortality. In COVID-19 infection, the high mortality in HD patients with high phosphorus levels at the time of diagnosis can be explained by the fact that these patients are currently at an increased risk for all-cause mortality because of the higher levels of phosphorus already. All these findings emphasise that HD patients are a distinct population and that specific studies should be conducted for this patient group, apart from community-based studies.

Conclusion

As a result, predicting mortality in HD patients with COVID-19 is of great importance in terms of both follow-up and treatment, providing additional benefits and increasing patient survival. Unfortunately, there are very few studies on this subject in the literature. Our study is the first one in the literature showing the effect of NLR, CRP/albumin, MPV and phosphorus levels on mortality. At the same time, these parameters are easily accessible and cost-effective. We believe that these parameters can be used to predict mortality in HD patients.

Limitations of the study

The limitation of this study is the small number of patients. The study was also planned retrospectively. We think that prospective studies with larger number of patients are needed.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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Authors' contribution

Data curation: Gulay Yilmaz, Ozge Timur.
Formal analysis: Ozge Timur.
Investigation: Gulay Yilmaz, Ozge Timur.
Methodology: Gulay Yilmaz.
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Software: Ozge Timur.
Supervision: Gulay Yilmaz, Ozge Timur.
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Visualization: Ozge Timur.
Writing–original draft: Gulay Yilmaz, Ozge Timur.
Writing–review & editing: Gulay Yilmaz.

Conflicts of interest

The authors declare that they have no competing interests. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This research project was also approved at the Ethics Committee of Erzurum Regional Training and Research Hospital on November 2, 2020 with approval number 2020/20-201. Accordingly, written informed consent was taken from all participants before any intervention. Additionally, ethical issues (including plagiarism, data fabrication, double publication) were completely observed by the authors.

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