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Evaluation of MULBSTA, SOFA, APACHE II scores and hematological parameters as predictors of mortality in COVID-19 pneumonia

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ABSTRACT

Aim: COVID-19 (coronavirus disease 2019) pneumonia is a serious condition with high mortality and morbidity. Tools are needed for effective diagnosis and better prediction of prognosis in the course of this disease. This study aimed to compare the effectiveness of the MuLBSTA (Multilobular infiltration, hypo-Lymphocytosis, Bacterial coinfection, Smoking history, hyper-Tension and Age) score with blood parameters, SOFA (Sequential Organ Failure Assessment), and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores, and to investigate its significance in predicting 28-day mortality in patients diagnosed with COVID-19 and followed up in the intensive care unit (ICU).

Material and Method: This study included 312 patients admitted to ICU for COVID-19 infection. SOFA, MuLBSTA and APACHE-II scores of patients were estimated at ICU admission. Demographic data and laboratory results of patients were retrospectively reviewed.

Results: Of the 312 patients included in the study, 58.7% (n=183) were male and 41.3% (n=129) were female. The AUC value was 0.863 for the SOFA score and 0.843 for the MuLBSTA score. The MuLBSTA score was positively correlated with the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), while it was negatively correlated with the lymphocyte-to-monocyte ratio (LMR). Patients were divided into two groups as high-risk and low-risk, considering a cut-off value of 12 for the MuLBTSA score. The survival time of patients with a high-risk MuLBTSA score was 12±0.78 days, while the survival time of patients with a low MuLBTSA score was 22.8±1.3 days.

Conclusion: The combined use of the MuLSBTA score, SOFA score, and NLR after ICU admission for COVID-19 pneumonia will be more effective in predicting mortality.

Keywords: APACHE II score, COVID-19 pneumonia, Neutrophil-to-lymphocyte ratio, MuLBSTA score, SOFA score

INTRODUCTION

Coronavirus disease (COVID-19) is caused by a novel coronavirus now known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (1). This disease caused by the SARS-CoV-2 infection was first reported in Wuhan, China in December 2019 (2). After the rapid spread of the disease, the World Health Organization (WHO) declared SARS-CoV-2 an epidemic and a global pandemic on 30 January 2020 (3).

Patients usually present to the hospital with fever, dry cough, dyspnea, headache, fatigue, and muscle and bone pain. Less common symptoms include sore throat, confusion, productive cough, hemoptysis, diarrhea, nausea, and chest pain. Although many COVID-19 patients are asymptomatic, some patients develop pneumonia. These patients have increased respiratory distress, with 10% of them requiring mechanical ventilation and intensive care admission (4). Signs of pneumonia include decreased oxygen saturation, abnormal blood gas, multifocal opacities, or ill-defined areas of segmental consolidation on chest X-ray or computed tomography (CT). Patients presenting to the hospital late or with severe illness usually suffer from acute respiratory distress syndrome (ARDS), acute respiratory failure, acute kidney injury, and multiple organ failure (4,5).

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The COVID-19 pandemic has caused an extremely significant increase in the global mortality rate. Between 2020 and 2021, COVID-19 resulted in 14.83 million deaths (13.23-16.58) (6). Tools for effective diagnosis and better prediction of prognosis are needed to mitigate the burden of this disease on the healthcare system (7).

The MuLBSTA (Multilobular infiltration, hypo-Lymphocytosis, Bacterial coinfection, Smoking history, hyper-Tension and Age) scoring system, one of the scoring systems used for this purpose, was defined by Guo et al. (8) and has a strong predictive ability for mortality in viral pneumonia. The MuLBSTA scoring system examines a population of patients with characteristics similar to those with COVID-19 pneumonia (9). This scoring system consists of 6 main parameters, including multilobar infiltration on CT, lymphocytopenia, bacterial co-infection, smoking history, hypertension, and age >65 years old. The MuLBSTA score can be calculated for each patient with the values of all parameters. A score of 12 and above has been reported to be significantly associated with higher 90-day mortality (8,9).

The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system is the most widely used disease severity scale in intensive care units (ICUs) worldwide. This system is composed of 12 parameters and is applied within the first 24 hours after ICU admission. A higher APACHE II score represents a more severe illness and a higher risk of in-hospital death (10). The Sequential Organ Failure Assessment (SOFA) score can be calculated at ICU admission and subsequently every 24 hours. This scoring system consisting of 6 parameters is used to assess the condition of patients admitted to ICU. Changes in the SOFA score show a strong correlation with ICU mortality (11).

Various blood parameters such as neutrophil count, lymphocyte count, monocyte count, platelet count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio are used in the diagnosis, follow-up, and prognosis of infections. These are simple and cost-effective tests that can be used to determine disease severity and clarify the treatment plan (12). Especially the neutrophil-to-lymphocyte ratio has been reported to be a predictor for the presence of in community-acquired pneumonia (13). The lymphocyte-to-monocyte ratio has been reported to have a prognostic value in the diagnosis of respiratory tract infections caused by viral infections associated with Haemophilus influenza (14). Moreover, it is believed that the platelet-to-lymphocyte ratio may be a novel indicator for predicting the prognosis of COVID-19 patients (15). Another study showed that an increase in PCO_2 concentration in COVID -19 patients, together with older age, high APACHE scores, low lymphocyte count, elevated NLR could predict mortality (16).

This study aimed to compare the effectiveness of the MuLBSTA score with blood parameters, and the SOFA and APACHE II scores, which are universally used in intensive care units, and to investigate its significance in predicting 28-day mortality in patients diagnosed with COVID-19 and followed up in ICU.

MATERIAL AND METHOD

The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (Date: 02.12.2022, Desicion No: 582). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Patients who were admitted to the intensive care unit of Burdur State Hospital for COVID-19 infection between July 2020 and September 2022 were included in the study. This single-center study retrospectively reviewed the data of the patients. The study included only those with positive reverse transcription-polymerase chain reaction (RT-PCR) results of nasopharyngeal and tracheal aspirate samples. Of the patients whose data were reviewed in the study, 2 patients under the age of 18 years, 6 pregnant patients, 18 patients with end-stage renal disease, 2 patients with liver failure, 8 patients with active malignancies, 1 patient who received active immunosuppressive therapy after transplantation, 33 patients with less than 24 hours of ICU stay due to death or transfer to the ward, and 26 patients with incomplete data were excluded from the study. A total of 312 patients who met the inclusion criteria were identified for statistics (shown in **Figure 1**).

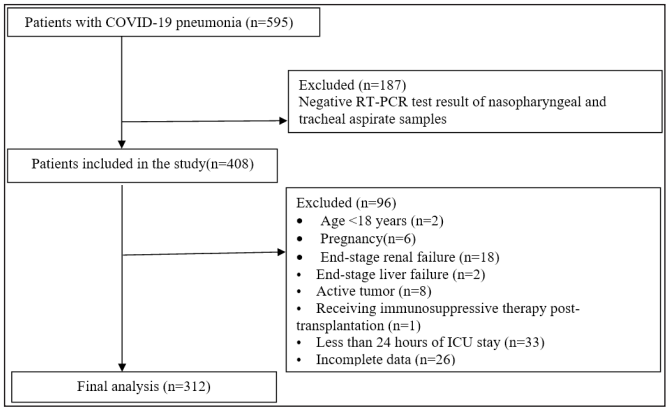

Figure 1. Flow chart of the study.
Abbreviations:COVID-19, coronavirus disease;RT-PCR, Reverse transcription-polymerase chain reaction; ICU, Intensive care unit.

Data Collection and Prognostic Scores

Data including demographic information, medical history, clinical findings, laboratory results, radiological images, and length of ICU stay were collected from

the medical electronic records of patients. Among the laboratory tests performed at ICU admission, leukocyte count, neutrophil count, lymphocyte count, monocyte count, platelet count, C-reactive protein (CRP), procalcitonin (PCT), ferritin, and D-dimer data were recorded. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, the lymphocyte-to-monocyte ratio (LMR) by dividing the absolute lymphocyte count by the absolute monocyte count, and the platelet/lymphocyte ratio (PLR) by dividing the absolute platelet count by the absolute lymphocyte count. SOFA scores (11), MuLBSTA scores (8), and APACHE II (10) scores were determined using standardized forms within 24 hours of admission. In addition, the length of ICU stay, requirement for mechanical ventilation, and time until death were recorded.

Statistical Analysis

Categorical variables were presented as percentages and frequencies. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to check whether continuous variables followed a normal distribution. Normally distributed continuous variables were presented as mean±standard deviation, while non-normally distributed continuous variables were presented as median and interquartile range (IQR). The chi-square test was used to compare categorical variables between groups. In the comparison of continuous variables, the independent samples t-test was used for normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. The Receiver operating characteristic (ROC) curve obtained by calculating the sensitivity and specificity for mortality was used to assess the performance of the tested scores. Youden's index was used to determine the optimal cut-off value based on the ROC analysis results. Survival analysis was carried out using the Kaplan-Meier method. Factors affecting survival were investigated by log-rank test. Spearman's correlation coefficient was calculated and reported to reveal the degree of association between the continuous variables included in the study. Analyses were conducted with the SPSS version 22.0 software package.

RESULTS

Of the patients included in the study, 58.7% (n=183) were male and 41.3% (n=129) were female. The median age of the study group was 75 years (IQR=19 years). During the intensive care follow-up, 66.3% (n=207) of our patients died, while 33.7% (n=105) were discharged. The comparison of these patients in terms of demographic characteristics, clinical characteristics, and laboratory results is shown in **Table 1**.

Table 1. Comparison of demographic characteristics, clinical characteristics and laboratory results of patients

	Survival Group (n=105)	Mortality Group (n=207)	p value
Age (years)	71 (62-81)	78 (67-85)	0.002*
Sex			0.904**
Male, n (%)	61 (33.3%)	122 (66.7 %)	
Female, n (%)	44 (34.1 %)	85 (65.9 %)	
CRP (min-max)	87.5 (51.5-136.5)	110 (60-178)	0.018*
Procalcitonin (min-max)	0.15 (0.03-0.60)	0.41 (0.14-1.37)	<0.001*
Ferritin (min-max)	399 (198.5-690)	550 (312-1051)	<0.001*
D-dimer (min-max)	502 (294.5-1182)	804 (390-1463)	0.006*
APACHE-II (min-max)	17 (15-21)	20 (17-25)	<0.001*
SOFA (min-max)	6 (5-8)	9 (8-11)	<0.001*
MuLBSTA (min-max)	11 (9-13)	15 (15-18)	<0.001*
NLR (min-max)	9.19 (5.41-14.6)	17.48 (11.85-25.11)	<0.001*
LMR (min-max)	2.15 (1.36-3.15)	1.44 (0.92-2)	<0.001*
PLR (min-max)	243.1 (159.2-369.8)	351.31 (243.3-481.4)	<0.001*

*Mann-Whitney U test, **Fisher's exact test
Abbreviations: CRP, C-reactive protein; APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio.

The ROC analysis results for APACHE II score, SOFA score, MuLBSTA score, NLR, LMR, and PLR are shown in **Table 2**. The AUC value was 0.863 for the SOFA score and 0.843 for the MuLBSTA score. The sensitivity and specificity of a cut-off value of 7.5 for the SOFA score to predict survival were 0.81 and 0.72, respectively, while

Table 2. Optimal cut-off values and ROC analysis results for APACHE II score, SOFA score, MuLBSTA score, NLR, LMR, and PLR

Risk Factor	AUC	95% CI	Cut-off	p-value	Sensitivity %	Specificity %
APACHE II score	0.675	0.612-0.734	17.50	0.000	0.73	0.54
SOFA score	0.863	0.820-0.906	7.50	0.000	0.81	0.72
MuLBSTA score	0.843	0.799-0.888	12.50	0.000	0.86	0.58
NLR	0.730	0.670-0.790	9.24	0.000	0.85	0.51
LMR	0.330	0.266-0.394	1.44	0.000	0.51	0.32
PLR	0.646	0.580-0.712	265.27	0.000	0.71	0.57

Abbreviations: APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio;AUC, area under the curve; CI, confidence interval.

the sensitivity and specificity of a cut-off value of 12.5 for the MuLBSTA score were 0.86 and 0.58, respectively. **Figure 2** and **Figure 3** show the ROC curves plotted to estimate ICU mortality.

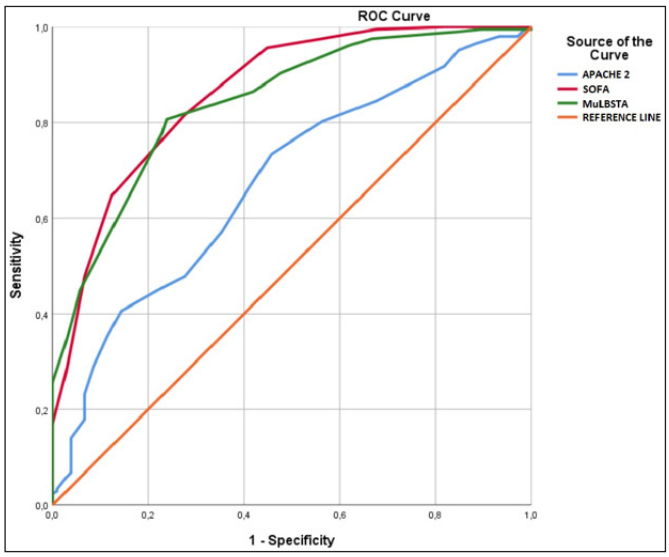

Figure 2. ROC analysis for APACHE II score, SOFA score, and MuLBSTA score.
Abbreviations: APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment.

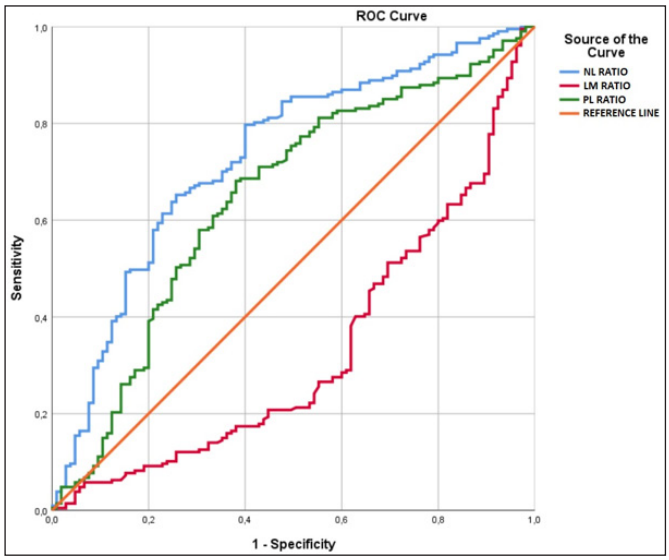

Figure 3. ROC analysis for NLR, LMR and PLR.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio.

NLR was positively correlated with CRP (r=0.152, p=0.007), procalcitonin (r=0.189, p=0.001), ferritin (r=0.159, P=0.005), D-dimer (r=0.161, p=0.004), SOFA score (r=0.199, p=<0.001), APACHE II score (r=0.147, p=0.009), and MuLBSTA score (r=0.342, p<0.001). LMR was negatively correlated with D-dimer (r=-0.139, p=0.039), SOFA score (r=-0.149, p=0.008), APACHE II score (r=-0.111, p=0.05), and MuLBSTA score (r=-0.234, p<0.001). On the other hand, PLR was positively correlated with only the MuLBSTA score (r=0.251, p<0.001). These results showed a positive correlation between the MuLBSTA score and NLR, PLR, and a negative correlation between the MuLBSTA score and LMR. The results of correlations between the variables are shown in **Table 3**.

Table 3. Correlations between variables

	NLR		LMR		PLR	
	r	p-value	r	p-value	r	p-value
CRP	0.152	0.007	0.036	0.52	0.075	0.187
Procalcitonin	0.189	0.001	-0.008	0.89	-0.043	0.448
Ferritin	0.159	0.005	-0.88	0.119	-0.006	0.917
D-dimer	0.161	0.004	-0.139	0.014	0.039	0.493
SOFA	0.199	<0.001	-0.149	0.008	-0.05	0.378
APACHE II	0.147	0.009	-0.111	0.05	0.025	0.661
MuLBSTA	0.342	<0.001	-0.234	<0.001	0.251	<0.001

Abbreviations: CRP, C-reactive protein; APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio.

Patients were divided into two groups as high-risk and low-risk, considering a cut-off value of 12 for the MuLBTSA score. The survival time of patients with a high-risk MuLBTSA score was 12±0.78 days, while the survival time of patients with a low-risk MuLBTSA score was 22.8±1.3 days. There was a statistically significant difference in survival between the groups with high and low-risk MuLBSTA scores (p<0.001). The Kaplan-Meier (K-M) survival curves for high-risk and low-risk groups are shown in **Figure 4**.

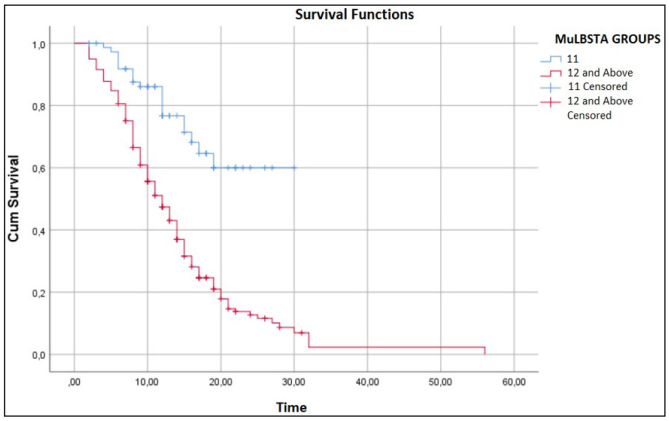

Figure 4. Kaplan-Meier survival curve of patients classified by MuLBSTA score.

DISCUSSION

COVID-19 has emerged as a disease with very high mortality and morbidity, causing very serious problems on a global scale. COVID-19 pneumonia has seriously increased the workload in intensive care units during the pandemic. During this period, some scoring systems and indicators have come to the fore in order to reduce the burden of these patients on the healthcare system, to select patients to be admitted to ICU, and to predict mortality.

In general, smokers, elderly population, patients with cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension, cancer or obesity have an increased risk of death due to SARS-CoV-2 infection (17). The prognosis of a disease becomes extremely important when so many factors play a role. The MuLBSTA scoring system is one of the tools that can help physicians in this decision-making process (18).

Elderly patients with COVID-19 have a higher mortality rate due to the high rate of symptomatic infection (19). Studies have confirmed the association between increased age and death in COVID-19 patients (19,20). Our study demonstrated a correlation between advanced age and mortality in COVID-19 disease (p=0.002).

Although COVID-19 infection may be a mild flu-like illness or be asymptomatic in most patients, a small proportion of patients may develop severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and even death. Various laboratory markers have been proposed for risk stratification in these patients. There is increasing evidence that features of hyperinflammation consisting of elevated serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia are seen in critically ill patients (7). A study by Cellina et al. (21) reported a significant increase in acute phase reactants such as CRP and D-dimer of patients with COVID-19 pneumonia in the mortality group. Similarly, in their meta-analysis investigating mortality factors for COVID-19 pneumonia, Li Zhang et al. (22) reported statistically higher CRP, PCT, and D-dimer levels in deceased patients than in the survival group.The results of our study also showed elevated levels of acute phase reactants, including CRP, PCT, D-dimer, and ferritin in the mortality group.

APACHE II and SOFA scores are well-known scoring systems that have been used for many years to evaluate critically ill patients and predict their mortality (23). Simple blood markers of NLR, LMR, and PLR are new biomarkers of systemic inflammation that are closely related to immune response (24). A study evaluating COVID-19 pneumonia in ICU patients reported statistically significantly higher APACHE II and SOFA scores in the deceased group than in the survival group (23). In their study investigating COVID-19 mortality, Citu et al. (25) reported a difference in NLR and MLR but no difference in PLR between the mortality and survival groups. Our study revealed a significant difference in APACHE II, SOFA scores, and NLR, LMR, and PLR values between the mortality group and the survival group.

A complete blood count is the cheapest, most accessible, and fastest diagnostic test among the markers that can be used. White blood cell, neutrophil, lymphocyte, and platelet counts and NLR, LMR, and PLR derived from these parameters provide us with rich information. There are studies showing that these hematological parameters especially predict inflammation (12,26). A study by Yanga et al. (12) evaluating NLR, LMR, and PLR to predict mortality of COVID-19 pneumonia by ROC analysis reported the AUC values as 0.841, 0.265, and 0.784, respectively. In our study, the AUC values for NLR, LMR, and PLR were found to be 0.730, 0.330, and 0.646, respectively. Based on our data, NLR and PLR were found to have a prognostic value, while LMR had no prognostic significance because its AUC value was less than 0.50. We are of the opinion that these simple biomarkers derived from hematological tests can be evaluated to predict the prognosis of COVID-19.

In our study, the AUC value was 0.863 for the SOFA score, 0.843 for the MuLBSTA score, and 0.673 for the APACHE II score. The sensitivity and specificity of the SOFA score to predict survival were 0.81 and 0.72, respectively, while the sensitivity and specificity of the MuLBSTA score were 0.86 and 0.58, respectively. In their study, Fayed et al. (27) reported an AUC value of 0.883 for the SOFA score in COVID-19 pneumonia, stating that it is a good predictor of mortality. Gowda et al. (28) reported an AUC value of 0.766 for the SOFA score, emphasizing that it is a better predictor than the APACHE2 score. Garcia et al. (29) found an AUC value of 0.777 for the MuLBSTA score to predict mortality in COVID-19 pneumonia, with a sensitivity of 0.683. In our study, the AUC value for the MuLBSTA score was 0.843, with a sensitivity of 0.86, while the AUC value for the SOFA score was 0.863, with a sensitivity of 0.81. Based on our results, we believe that the MuLBSTA and SOFA scores are better predictors of mortality than the APACHE II score.

A study by Peng et al. (30) evaluating the diagnostic data of hematological parameters in COVID-19 pneumonia reported a positive correlation between NLR and the MuLBSTA score. In our study, NLR was positively correlated with MuLBSTA and SOFA scores.

Guo et al. (8) divided the patients into two groups according to their MuLBSTA scores and classified those with a score of 0-11 as the low-risk group (mortality rate of 5.07%) and those with a score of 12-22 as the high-risk group (mortality rate 33.92%) and reported that the MuLBSTA score was a good predictor of prognosis. In a study by Preetam et al. (17), they compared the 14-day risk of mortality in both groups and showed an strong association in patients with a MuLBSTA score ≥12. Another study showed that COVID-19 patients with a

higher admission MuLBSTA score had a higher risk of death. In this study, it was shown that the ≥12 MuLBSTA score had a specificity of 89.5% and a sensitivity of 100% in predicting mortality (31). Our study revealed a statistically significant difference in survival between the groups with high and low-risk MuLBSTA scores ($p<0.001$).

There are several limitations to the present study. First of all, the study is a single-center study. The second limitation is the retrospective design of the study. The third limitation is the MuLSBTA score, which was originally defined as a predictor of 90-day mortality. In our study, 28-day mortality was evaluated due to the difficulty in reaching patients during the pandemic.

CONCLUSION

COVID-19 pneumonia is a global public health threat that causes very serious health problems due to its spread rate and course. It has been clearly seen during the pandemic that early diagnosis and prediction of prognosis are very important. These prognostic predictions are also gaining importance in intensive care clinics. The MuLBSTA scoring system is a good tool to predict the mortality of COVID-19 pneumonia. Especially patients with a score ≥12 are associated with poor prognosis. SOFA, a conventional intensive care scoring system, also provides significant guidance in this respect. NLR obtained from hematological parameters also yielded significant results. The combined use of the MuLSBTA score, SOFA score, and NLR after ICU admission in COVID-19 pneumonia will be more effective in predicting.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (Date: 02.12.2022, Desicion No: 582).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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