Tech Science Press

Diagnostic and prognostic significance of the lymphocyte/C-reactive protein ratio, neutrophil/lymphocyte ratio, and D-dimer values in patients with COVID-19

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Abstract: In this study, our aim was to examine the diagnostic and prognostic significance of lymphocyte/C-reactive protein ratio (LCR), neutrophil/lymphocyte ratio (NLR) and D-dimer parameters in COVID-19 infection. The LCR, NLR, neutrophil count, mean platelet volume (MPV), C-reactive protein (CRP), and D-dimer parameters were evaluated retrospectively. This was a retrospective cohort study with 1000 COVID-19 positive and 1000 healthy control groups, all over the age of 18 years. Odds ratio (OR) and 95% confidence interval (CI) values were calculated for each parameter found to be statistically significant in the univariate and multivariate logistic regression models. Herein, 127 (12.7%) of the COVID-19^{+} patients, whose data was included in this study, died. The neutrophil, MPV, CRP, D-dimer, and NLR values were higher in the COVID-19^{+}/deceased group than in the COVID-19^{+}/alive and control groups ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$). The lymphocyte and LCR values were lower in the COVID-19^{+}/deceased group than in the COVID-19^{+}/alive and control groups ($p < 0.001$, $p < 0.001$). Variables with statistically significance in predicting COVID-19 infection were lymphocyte, LCR, D-dimer, NLR, CRP, MPV, PLT, and neutrophil values. Statistically significant variables in predicting mortality due to COVID-19 were LCR, CRP, NLR, lymphocyte, D-dimer, neutrophil, and MPV values. A low LCR and high NLR are associated with the presence, prognosis, and mortality due to COVID-19. LCR and NLR parameters can thus be used in clinical monitoring to reduce morbidity and mortality rates.

INTRODUCTION

China announced the outbreak of a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December, 2019 (Guan *et al.*, 2020), and the disease was declared a pandemic by the World Health Organization (WHO) in March, 2020 (Cucinotta and Vanelli, 2020). Globally, as of 7:03 pm CEST, September 20, 2021, there have been 228,394,572 confirmed cases of COVID-19, including 4,690,186 deaths, as reported by the WHO. As of September 19, 2021, a total of 5,771,619,897 vaccine doses have been administered (https://covid19.who.int/). Coronavirus 2019 (COVID-19) infection can initiate with flu-like common symptoms (Aktas, 2020); however, ~10% of symptomatic patients develop a more severe disease (Lavezzo *et al.*, 2020). Symptoms of COVID-19 infection, such as fever, weakness, loss of taste and smell, and cough, are observed in clinical practice. Although thorax computed tomography findings progress in the first days of this disease, the prognosis is often good (Chan *et al.*, 2020). Acute respiratory distress syndrome and mortality are observed in patients with a more severe disease (Chen *et al.*, 2020).

The most effective method for the diagnosis of COVID-19 infection is the detection of viral nucleic acid using reverse transcription-polymerase chain reaction (RT-PCR). Laboratory findings and radiology tests confirm the clinical diagnosis (Yang *et al.*, 2020). As in all viral infections, changes in hematological laboratory parameters are observed in patients with COVID-19. A high neutrophil count and lymphopenia are among the common ones (Carpio-Orantes *et al.*, 2020). the neutrophil/lymphocyte ratio (NLR), platelet (PLT)/lymphocyte ratio (PLR), and mean platelet volume (MPV)/PLT ratios in peripheral blood are reported to be the indicators of the infection type and prognosis (Ugurlu *et al.*, 2021).

C-reactive protein (CRP) is a commonly used inflammatory marker. Moreover, CRP or its derivates have been suggested to be

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associated with chronic low inflammatory conditions (Aktas, 2021). CRP is present in very low levels or even absent in healthy individuals. Significantly elevated CRP levels are observed in conditions such as infection and trauma (Bal et al., 2021).

NLR, PLR, and high CRP are also reported as prognostic indicators in systemic inflammatory diseases. Elevated CRP level is also observed in patients having COVID-19 (Aktas, 2021). Studies have shown that the correlation of lymphocyte/CRP ratio with clinical severity is superior to NLR in COVID-19 patients (Bal et al., 2021; Lagunas-Rangel, 2020). Similar to CRP, elevated D-dimer value is a typical phenomenon in patients with COVID-19 (Wang et al., 2011).

The NLR is a novel inflammatory predictor derived from routine hemogram tests. It has been associated with various clinical inflammatory conditions, including irritable bowel disease (Aktas et al., 2020), thyroiditis (Aktas et al., 2017), type 2 diabetes (Duman et al., 2019), diabetic nephropathy (Bilgin et al., 2020), malignancy (Sit et al., 2019), and COVID-19 infection (Yildiz et al., 2021). Similarly, the PLR is a novel predictor of the inflammatory burden and has been reported to be associated with COVID-19 infection (Aktas, 2021), diabetes mellitus (Atak et al., 2019), and cancer (Atak et al., 2021). The MPV is the first studied hemogram-derived inflammatory marker and is reported to be associated with the inflammatory burden in functional bowel diseases (Aktas et al., 2014), type 2 diabetes mellitus (Cakir et al., 2014), infections (Aktas et al., 2013), rheumatoid arthritis (Cakir et al., 2020), vertebral disc hernia (Dagistan et al., 2016), dementia (Dagistan and Cosgun, 2019), cardiac conditions (Sincer et al., 2018), obesity (Aktas et al., 2018) and frailty (Bilgin et al., 2021).

The prognostic and diagnostic association of these parameters with COVID-19 remains unclear (Bal et al., 2021; ElshazliI et al., 2020). The present study compared the lymphocyte/CRP ratio (LCR), NLR, neutrophil count, MPV, PLT, neutrophil, CRP, and D-dimer values in patients with COVID-19 and a non-COVID-19 control group. Hence, the present study aimed to reveal their significance in patients with COVID-19.

Materials and Methods

Study design and participants

The laboratory data of 1,000 patients diagnosed with COVID-19 and hospitalized at the Erbaa State Hospital (Erbaa, Turkey) between April 1, 2020, and April 01, 2021, were used. The LCR, NLR, neutrophil count, MPV, PLT, neutrophil, CRP, and D-dimer values of these patients were evaluated retrospectively. Laboratory data were obtained from the electronic information system of the hospital. Patients with a confirmed diagnosis of COVID-19 through RT-PCR were included in the present study. Complete blood count, biochemical tests, and D-dimer were determined with Mindray BC 6000 (Mindray Global, Shenzhen, China), Beckman Coulter AU680 (Beckman Coulter, California, USA) and Succeeder Sf 8100 (Beijing Succeeder Technology Inc., Beijing, China), respectively. Further, the differences in the values between the COVID-19^{+} patients as well as those of 1,000 healthy controls, whose parameters were previously measured at the hospital, were investigated. This was a retrospective cohort study with patients over 18 years of age (Fig. 1).

STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Ethical considerations

An application was made to the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (as Erbaa State Hospital, in Erbaa, Tokat Province, Turkey), and the necessary approval was obtained from the ethics committee (approval date, August 17, 2021; decision number, HRU/ 20.14.13). The study was carried out in compliance with the ethical principles of the Declaration of Helsinki.

Statistical analysis

The data collected in the present study were statistically analyzed using IBM SPSS Statistics for Windows 22.0. Proportion comparisons between the research groups were made using the Chi-squared test. The normality distribution of the data was evaluated using the Kolmogorov-Smirnov test. Levene's test was used to test the homogeneity of the variances. The Student's t-test was used to compare the normally distributed data between two independent groups, and the Mann-Whitney U test was performed to compare the non-normally distributed data. To determine the differences between groups following ANOVA, Tukey's post hoc test was used when the assumption of homogeneity of the variances was met, and the Games-Howell post hoc test was used when it was not. Receiver operating characteristic (ROC) analysis was used to determine whether age, sex, and certain laboratory parameter values could be prognostic indicators for the COVID-19 positivity and mortality of the COVID-19^{+} study participants. The ROC curves, area under the curve (AUC), and 95% confidence interval (CI) values were calculated. The AUC values obtained in the analyses were classified as follows: 0.9–1, excellent; 0.8–0.9, good; 0.7–0.8, fair; 0.6–0.7, poor; and 0.5–0.6, unsuccessful. Youden index (maximum sensitivity and specificity) was used to find the optimal cut-off point in the ROC analysis. According to the univariate analysis, all the variables related to COVID-19-associated mortality, at a significance level of <0.10, were included in the multivariate binary logistic regression model. The odds ratio (OR) and 95% CI values were calculated for each statistically significant parameter in the univariate and multivariate logistic regression models. A value with $p < 0.05$ was considered to indicate a statistically significant difference.

Results

In the study, the data of 2,000 participants, 1,000 of whom were in the control group and 1,000 patients positive for COVID-19, were analyzed retrospectively. Of the COVID-19^{+} patients, 873 (87.3%) survived, and 127 (12.7%) succumbed to the disease. In addition, while a mutant variant (non-alpha) was detected in 55 (5.5%) patients, the mutant variant was not observed in 945 (94.5%) patients. The sex ratios were statistically similar between the study groups ($p = 0.053$): 52.9% of the participants in the control group were female ($n = 529$) and 47.1% were male ($n = 471$); 50.5% of the patients in the
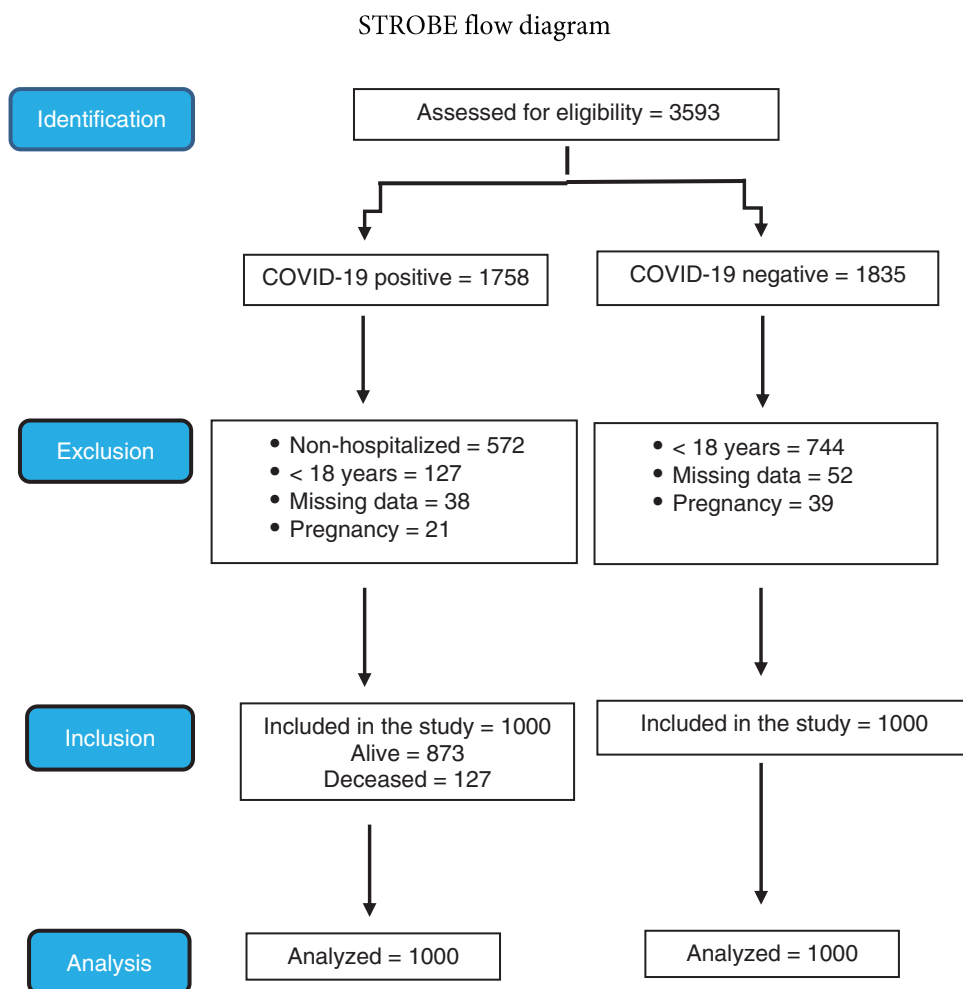
STROBE flow diagram

FIGURE 1. Recruitment and assessment flowchart for the patients and healthy controls.

COVID-19[+]/alive group were female ($n = 441$) and 49.5% were male ($n = 432$); 41.7% of the patients in the COVID-19^{+}/deceased group were female ($n = 53$) and 58.3% ($n = 74$) were male. The difference between the duration of hospitalization of the patients who survived and those who succumbed to COVID-19 was not statistically significant ($p = 0.062$). The mean length of hospital stay of the survivors was 7.72 ± 5.47 days [median (min-max), 7 (0–79) days], and the mean of the number of patients hospitalized among those who did not survive was 9.09 ± 6.23 [median (min-max), 8 (1–30)]. The difference in the mean age of the study participants was statistically significant ($p < 0.001$). According to the post hoc test results, the mean age of the deceased participants was significantly higher than that of the subjects in the control group and the survivors ($p < 0.001$ and $p < 0.001$) (Table 1). The mean age of the survivors was also significantly higher than that of the subjects in the control group ($p < 0.001$; Table 1).

The results of the statistical analysis of the comparisons of the LCR, NLR, neutrophil, lymphocyte, PLT, MPV, CRP, and D-dimer values between the groups are presented in Table 1. Box plots of the distribution of the neutrophil, lymphocyte, LCR, CRP, MPV, PLT, and D-dimer values among the research groups are illustrated in Figs. 2 and 3. The differences in the LCR, NLR, neutrophil, lymphocyte, PLT, MPV, CRP, and D-dimer values were statistically significant between the study groups ($p < 0.001$). According to the post hoc test results, the neutrophil, MPV, CRP, D-dimer, and NLR values were significantly higher in the COVID-19^{+}/deceased group than in the COVID-19^{+}/alive and control groups ($p < 0.001$). These values were also significantly higher in the COVID-19^{+}/alive group compared with the control group ($p < 0.001$). The lymphocyte and LCR values were significantly lower in the COVID-19^{+}/deceased group than in the COVID-19^{+}/alive and control groups ($p < 0.001$). These values were also significantly lower in the COVID-19^{+}/alive group than in the control group ($p < 0.001$). The PLT values were significantly higher in the control group than in the COVID-19^{+}/deceased and COVID-19^{+}/alive groups (p-values were $p = 0.012$ and $p < 0.001$, respectively). No statistically significant differences were observed in the PLT values between the COVID-19^{+}/deceased and COVID-19^{+}/alive groups ($p = 0.850$).

ROC analysis was then performed to determine the efficiency of using the LCR, NLR, neutrophil, lymphocyte, PLT, MPV, CRP, and D-dimer values in predicting COVID-19 prognosis and mortality. The sensitivity and selectivity values calculated according to the AUC values and cut-off points with 95% CI values are presented in Table 2. The ROC curve is illustrated in Fig. 4. The ROC analysis indicated that all parameters were statistically significant ($p < 0.001$, Table 2). According to the AUC

TABLE 1

Comparison of the sex, age, neutrophil, lymphocyte, PLT, MPV, CRP, D-dimer, NLR, and LCR values between research groups

Parameter reference ranges	Control (1) (n = 1,000)	COVID-19[+]/alive (2) (n = 873)	COVID-19[+]/deceased (3) (n = 127)	p-value	Post hoc p-value
Sex (female/male)	529/471 (52.9/47.1%)	441/432 (50.5/49.5%)	53/74 (41.7/58.3%)	0.053[a]	–
Age (years)	40.61 ± 13.72	59.97 ± 17.38	73.92 ± 9.73	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
Neutrophil (1.82–7.42) (10^9/L)	4.47 ± 3.01	5.25 ± 3.29	7.63 ± 4.88	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
Lymphocyte (0.85–3.00) (10^9/L)	3.05 ± 1.15	1.45 ± 0.91	1.03 ± 0.78	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
PLT (151–304) (10^9/L)	258.3 ± 85.9	229.1 ± 94.8	233.8 ± 100	<0.001[b]	1–2: <0.001[d] 1–3: 0.012[d] 2–3: 0.850[d]
MPV (9.7–11.9) (fL)	9.12 ± 2.08	10.01 ± 1.17	10.47 ± 1.23	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
CRP <5 mg/L	1.09 ± 0.09	5.66 ± 4.69	9.79 ± 4.50	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
D-dimer 0.00–0.50 µg/mL	0.16 ± 0.08	0.55 ± 0.64	1.01 ± 0.92	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
NLR	2.82 ± 9.32	5.51 ± 6.98	12.29 ± 11.73	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
LCR	2.80 ± 1.10	1.40 ± 2.99	0.27 ± 0.61	<0.001[b]	1–2: <0.001[c] 1–3: <0.001[c] 2–3: <0.001[c]
Hospital duration (days)	–	7.72 ± 5.47	9.09 ± 6.23	>0.05	2–3: >0.05[c]

Notes: [a]Data were analyzed using the Chi-squared test; [b]data were analyzed using ANOVA; [c]data were analyzed using Games-Howell post-hoc multiple comparison tests; [d]data were analyzed using Tukey's post-hoc multiple comparison tests. NLR, neutrophil/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; CRP, C-reactive protein; MPV, mean platelet volume; PLT, platelet.

values, statistically significant variables in predicting COVID-19 included lymphocyte, LCR, D-dimer, NLR, CRP, MPV, PLT, and neutrophil values. The success of using the lymphocyte, LCR, D-dimer, and NLR values in predicting COVID-19 positivity was good, while that of using the CRP value was fair. The success of using the MPV and PLT values was poor. The neutrophil value was found to be not of use. The sensitivity and selectivity levels calculated according to the cut-off points determined using the Youden index were calculated only for the parameters with good AUC values and are presented in Table 2.

ROC analysis was also performed to determine the efficiency of using the LCR, NLR, neutrophil, lymphocyte, PLT, MPV, CRP, and D-dimer values in predicting mortality in patients with COVID-19. The sensitivity and selectivity values calculated according to the AUC values and cut-off points with 95% CIs are presented in Table 3. The ROC curve is illustrated in Fig. 5. As a result of the ROC analysis, all the parameters apart from the PLT count ($p = 0.723$) were found to be statistically significant ($p < 0.001$, Table 3). Statistically significant variables in predicting COVID-19-associated mortality based on the AUC value were LCR, CRP, NLR, lymphocyte, D-dimer, neutrophil, and MPV. The use of LCR, CRP, and NLR values was fairly successful. The success of using the lymphocyte, D-dimer, neutrophil, and MPV values was poor. The sensitivity and selectivity levels calculated

according to the cut-off points determined using the Youden index were calculated only for parameters with fair AUC values and are presented in Table 3.

The results of the univariate and multivariate binary logistic regression analysis performed to determine the factors affecting mortality and the OR values in the COVID-19^{+} patients are presented in Table 4. Sex, age, the duration of hospitalization, the mutant variant, and the LCR, CRP, and NLR values, which were significant ($p < 0.01$) in the univariate model, were included in the multivariate model. The final model created by subtracting the sex, mutant variant, duration of hospitalization, and CRP value, which were insignificant in the multivariate model, is presented in Table 4. According to the model results, being 1 unit older in the COVID-19^{+} patients increased the probability of mortality (OR, 1.06; 95% CI, 1.05–1.08). A 1-unit lower LCR in the COVID-19^{+} patients increased the probability of mortality (OR, 3.27; 95% CI, 1.99–5.36), while an NLR > 1 unit in these patients increased the probability of mortality (OR, 2.36; 95% CI, 1.50–3.71) (Table 4).

Discussion

The hematological laboratory parameters of COVID-19 patients also exhibit significant changes. The LCR and NLR ratios are parameters that have been reported to indicate the
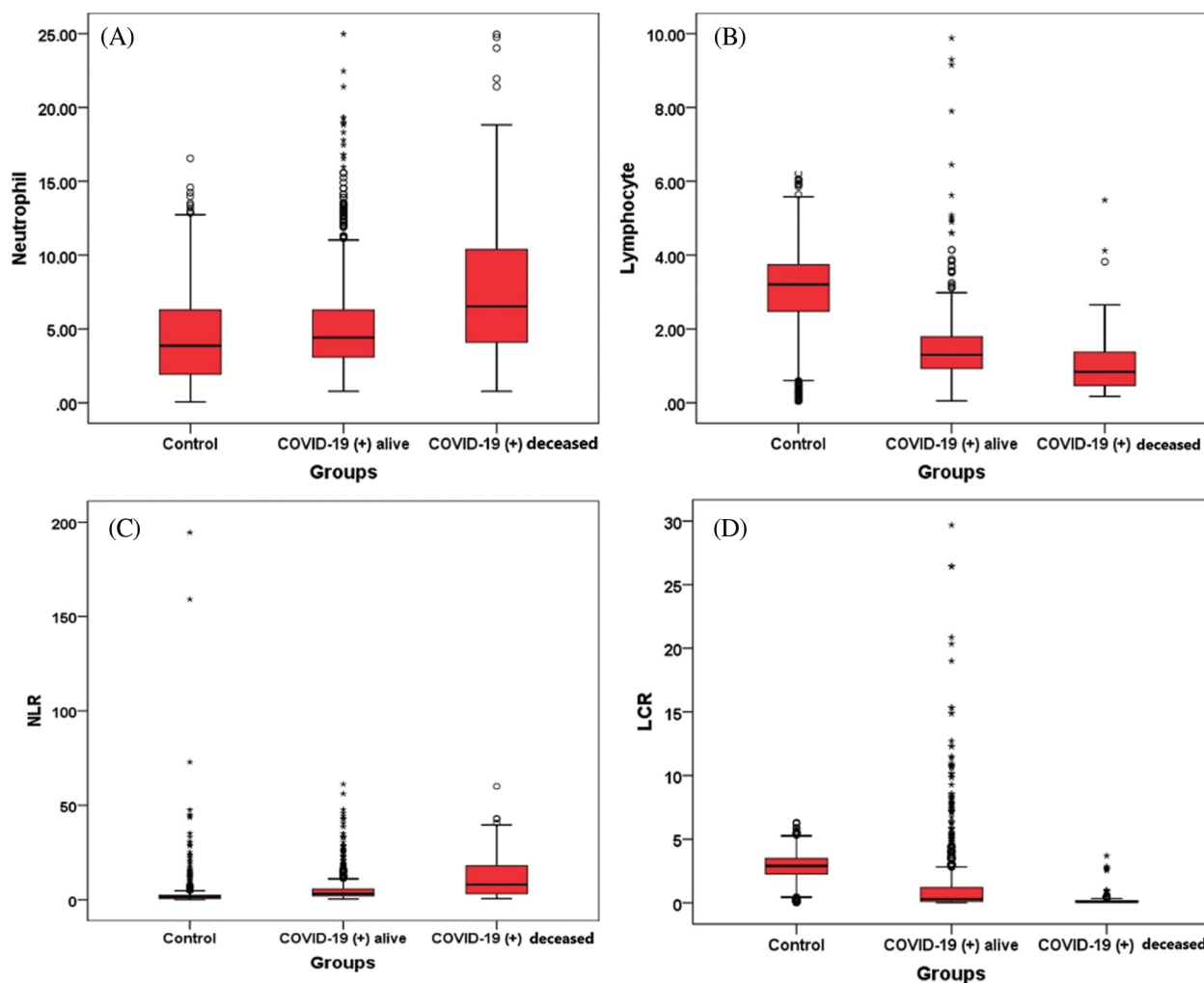
FIGURE 2. Boxplot of the distribution of the (A) neutrophil, (B) lymphocyte, (C) NLR, and (D) LCR values among the research groups. NLR, neutrophil/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio.

type of infection and prognosis (Carpio-Orantes et al., 2020; Ugurlu et al., 2021; Bal et al., 2021). The prognostic significance of LCR and NLR has also been reported in acute conditions other than COVID-19 (such as acute appendicitis and acute thyroiditis) (Ugurlu et al., 2021; Aktas et al., 2017) and in intensive care patients (Salciccioli et al., 2015; Wang et al., 2017).

In the present study, 2,000 participants, including 1,000 patients hospitalized due to COVID-19 and 1,000 healthy controls, were analyzed retrospectively. The neutrophil, MPV, CRP, D-dimer, and NLR values were significantly higher in the deceased patients than in the survivors and the control group. However, the LCR and lymphocyte values were significantly lower in this group when compared with the other two groups. The success of these parameters in predicting COVID-19 positivity, in descending order, were lymphocyte, LCR, D-dimer, NLR, CRP, MPV, PLT, and neutrophil values. The success of using the lymphocyte, LCR, D-dimer, and NLR values in predicting COVID-19 positivity was good. The success of these parameters in predicting COVID-19 mortality, in descending order, were LCR, CRP, NLR, lymphocyte, D-dimer, neutrophil, and MPV values.

In their study, Liu et al. (2020) reported hospital mortality at a rate of 13.47% for 245 patients with COVID-19, similar to the present study. Their study reported that a high NLR was

significantly associated with hospital mortality, and each 1-unit increase in the NLR increased mortality by 1.1; in the present study, this rate was 2.36. Moreover, herein, we observed that the lymphocyte and PLT counts were not associated with hospital mortality. In addition, herein, the lymphocyte count was significantly lower in the patients who succumbed to COVID-19 when compared with the other groups. Likewise, no significant association was found between the PLT count and mortality rates. In the present study, it was observed that having a high NLR was a predictor of in-hospital mortality in patients diagnosed with COVID-19 and also determined high-risk patients.

Ye et al. (2020) reported a hospital mortality rate of 14.9% in their study of 349 hospitalized patients with COVID-19, which was similar to that determined herein. Their study also reported that the NLR and D-dimer parameters were highly associated with mortality (Yan et al., 2020). Herein, the D-dimer and NLR values were significantly higher in the COVID-19^{+}/deceased group than in the COVID-19^{+}/alive and control groups ($p < 0.001$); besides, the success of these parameters in predicting COVID-19 positivity was good.

In the study by Jimeno et al. (2021), comprising 119 patients with COVID-19, a high NLR was associated with clinical severity and mortality, consistent with those found herein.
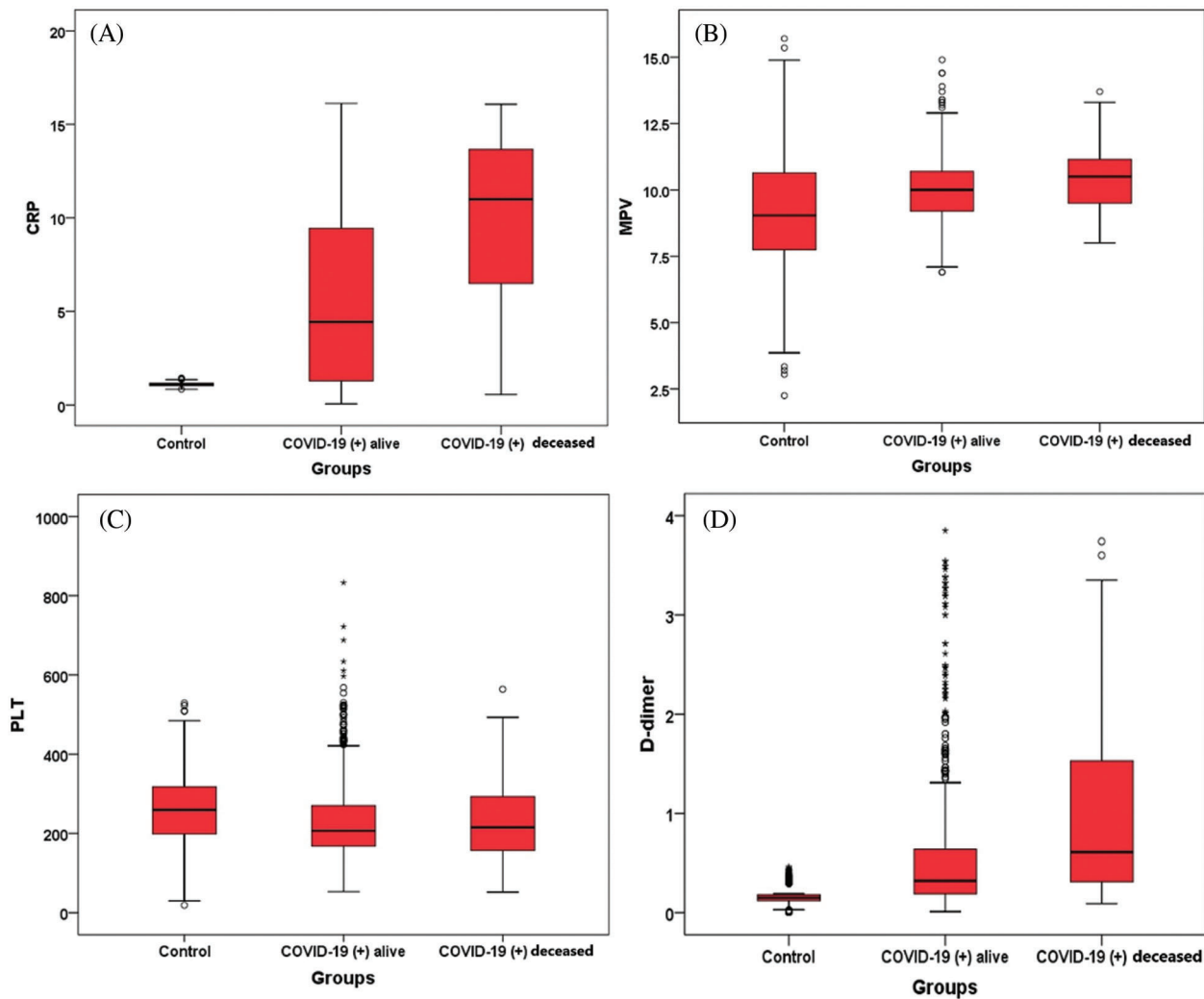
FIGURE 3. Boxplot of the distribution of the (A) CRP, (B) MPV, (C) PLT, and (D) D-dimer values among the research groups. CRP, C-reactive protein; MPV, mean platelet volume; PLT, platelet.

TABLE 2

ROC analysis results for COVID-19 positivity

Variables	Area	95% CI		p-value	Cut-off	Sensitivity	Specificity
		Lower bound	Upper bound				
Lymphocyte	0.874	0.856	0.892	<0.001	2.08	85.9%	88.0%
LCR	0.853	0.834	0.872	<0.001	1.69	81.6%	89.3%
D-dimer	0.828	0.809	0.846	<0.001	0.19	76.0%	83.8%
NLR	0.802	0.783	0.821	<0.001	2.13	75.5%	71.9%
CRP	0.794	0.769	0.818	<0.001	1.36	76.3%	99.8%
MPV	0.653	0.628	0.678	<0.001	–	–	–
PLT	0.626	0.602	0.651	<0.001	–	–	–
Neutrophil	0.597	0.572	0.622	<0.001	–	–	–

Notes: ROC, receiver operating characteristic; AUC, area under the curve, CI, confidence interval; NLR, neutrophil/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; CRP, C-reactive protein; MPV, mean platelet volume; PLT, platelet.

In the study by Yan *et al.* (2020), which included 191 patients with COVID-19, the NLR, and CRP values were significantly higher, and the lymphocyte values were significantly lower in the patient group. In the study by Seyit *et al.* (2020) on 110 patients with COVID-19, the NLR, and CRP values were significantly higher in the patient group than in the healthy control group. The optimal cut-off values of these parameters were reported as 0.615 and 0.691, respectively (Seyit *et al.,* 2020), while in the present study, these values were 2.13 and 1.36, respectively.
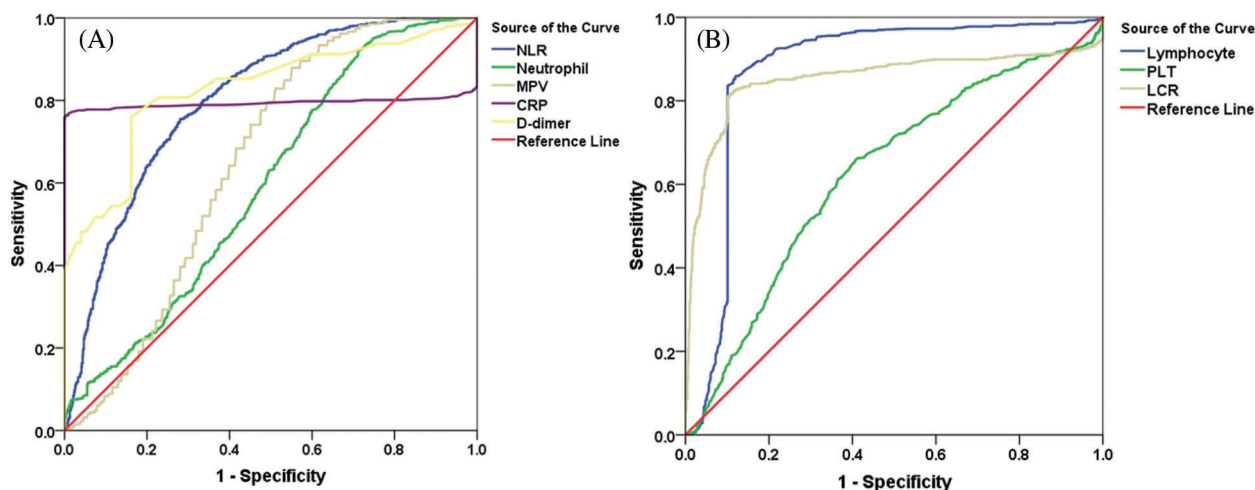
FIGURE 4. ROC curves for the (A) NLR, neutrophil, MPV, CRP, and D-dimer values, and (B) lymphocyte, PLT and LCR values in the prediction of COVID-19 positivity. NLR, neutrophil/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; CRP, C-reactive protein; MPV, mean platelet volume; PLT, platelet.

TABLE 3

ROC analysis results for the mortality of the COVID-19$^+$ participants

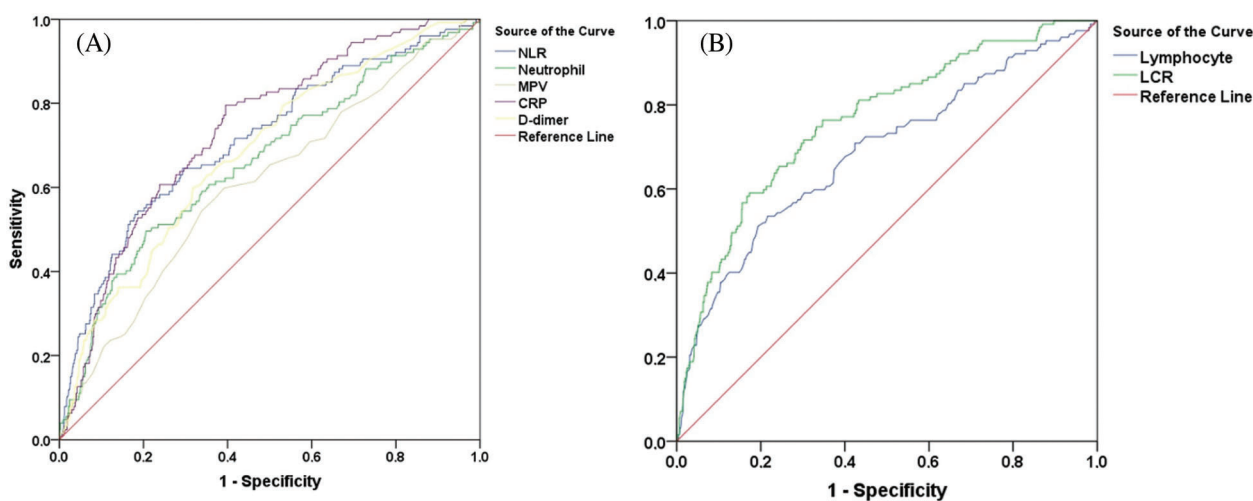| Variables	AUC	95% CI		p-value	Cut off	Sensitivity	Specificity
		Lower bound	Upper bound				
LCR	0.763	0.718	0.808	<0.001	0.169	76.4%	65.3%
CRP	0.738	0.694	0.782	<0.001	6.225	79.5%	60.5%
NLR	0.714	0.663	0.765	<0.001	7.303	54.3%	81.3%
Lymphocyte	0.687	0.633	0.741	<0.001	–	–	–
D-dimer	0.683	0.634	0.731	<0.001	–	–	–
Neutrophil	0.661	0.608	0.715	<0.001	–	–	–
MPV	0.608	0.554	0.661	<0.001	–	–	–
PLT	0.510	0.452	0.568	0.723	–	–	–

FIGURE 5. ROC curves for the (A) NLR, neutrophil, MPV, CRP, and D-dimer values, and (B) lymphocyte and LCR values in the mortality of the COVID-19$^+$ participants. NLR, neutrophil/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; CRP, C-reactive protein; MPV, mean platelet volume; PLT, platelet.

TABLE 4

Univariate and multivariate logistic regression analysis results of the mortality of COVID-19^{+} participants

	Univariate		Multivariate	
	p-value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)
Sex	0.065	–	ns	–
Age, years	<0.001[a]	1.07 (1.05–1.09)	<0.001[a]	1.06 (1.05–1.08)
Duration of hospitalization	0.015[a]	1.03 (1.01–1.07)	ns	–
Mutant (no reference value for mutant: yes)	0.037[a]	8.30 (1.13–60.58)	ns	–
LCR <0.169 (reference value for LCR: >0.169	<0.001[a]	6.08 (3.95–9.37)	<0.001[a]	3.27 (1.99–5.36)
CRP >6.225 (reference value for CRP: <6.225	<0.001[a]	5.95 (3.78–9.34)	ns (0.094)	–
NLR >7.303 (reference value for NLR: <7.303	<0.001[a]	5.18 (3.51–7.64)	<0.001[a]	2.36 (1.50–3.71)

Nagelkerke R Square: 0.278, Cox and Snell R square: 0.148, Hosmer and Lemeshow tests: Chi square = 11.546, df = 8, *p* = 0.173, Classification success rate: 87.7%

Notes: [a]Indicates statistically significant differences. ns, not significant; NLR, neutrophil/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; CRP, C-reactive protein.

In a previous retrospective study conducted by Shang *et al.* (2020), which included 443 patients with COVID-19, the NLR, PLT and CRP values were found associated with disease severity, and the NLR was the most effective marker among them. In the present study, the NLR was also associated with mortality, although the LCR was more valuable in this regard.

In the study by Ding *et al.* (2020), comprising 72 patients with COVID-19, the leukocyte, neutrophil, and NLR values were significantly higher, and the lymphocyte counts were significantly lower in patients with the non-severe disease. In this respect, their results were compatible with those reported herein. Their study reported that the NLR was associated with the length of hospital stay and disease severity. The NLR and other parameters examined in the current study were found to not affect the duration of hospitalization.

In another study by Yang *et al.* (2020) on 69 patients with non-critical and 24 with critical COVID-19 infection, age, leukocyte count, NLR, the lymphocyte-monocyte ratio, PLR, and CRP were reported to be significantly higher than the other patients with non-critical COVID-19 infection. By contrast, the lymphocyte count was significantly lower. In addition, their study reported that the NLR was associated with clinical severity and disease prognosis and could be used as a marker in clinical applications. The most notable difference between their study and the current one was that the LCR was not examined. Apart from that, similar results were obtained.

Kong *et al.* (2020) also examined the NLRs of 210 patients with COVID-19 and reported that they were associated with disease severity following linear regression analysis (β = 0.056 and *p* = 0.000). They also demonstrated that the NLR was higher in the patient group with severe disease than in the group with mild disease (6.6 *vs.* 3.3, *p* < 0.001). Qin *et al.* (2020) reported that the NLR increased in patients with COVID-19 and could aid in diagnosis and treatment in the early period. These findings were consistent with those determined in the present study.

Bal *et al.* (2021) investigated 61 patients with COVID-19 and reported significantly decreased LCR in the patient group when compared with the healthy group and could be used to distinguish those with critical illness from the severely ill group (cut-off value, 43.21; sensitivity, 84%; specificity, 69%). The LCR (ROC AUC, 0.820) was observed to be more effective than the NLR (0.751) in distinguishing these patient groups. Similarly, in the present study, the LCR was more valuable than the NLR in predicting the disease and mortality.

The NLR is an easy-to-obtain marker and is elevated in a number of inflammatory conditions (Qin *et al.*, 2020). The NLR increases following an increase in the neutrophil count and a decrease in the lymphocyte count. An increase in the number of neutrophils occurs due to systemic inflammation. The lymphocyte count may decrease due to bone marrow suppression, stimulation of apoptosis, increased lymphocyte destruction, and sequestration to the lungs. The mechanism of this association between the neutrophils and lymphocytes has not been precisely unraveled yet. While neutrophils play a crucial role in innate immunity, lymphocytes play an essential role in adaptive immunity (Liu *et al.*, 2016). Lymphocytes are cells that regulate both cellular and humoral immunity and tend to decrease continuously in long-lasting inflammations. In addition, lymphocytes are responsible for destroying virus-infected cells. However, the role of neutrophils in defense against viral infections is not clear (Henry *et al.*, 2020; Camp and Jonsson, 2017). The neutrophil infiltration seen in patients with acute respiratory distress syndrome supports the hypothesis of the possible role of neutrophils in anti-viral protection.

The LCR is one of the novel markers for systemic inflammation, similar to the NLR (Okugawa *et al.*, 2021). It is calculated from the lymphocyte count and CRP value. The current study showed that the LCR was more significant than the NLR in predicting the presence of COVID-19 and mortality. The reason for the lower LCR in critically ill patients may be the decrease in the lymphocyte count following immune dysfunction and a higher CRP value in proportion to the severity of systemic inflammation.

D-dimer, which occurs after fibrin destruction, is significantly increased after microthrombotic events in peripheral blood vessels in patients with COVID-19 (Jin *et al.*, 2020). In our

study and other studies, D-dimer was found to be significant as a potential biomarker in predicting mortality and prognosis (Liu *et al.*, 2020; Fu *et al.*, 2020). The D-dimer elevation is likely to be associated with resistant hypoxemia, respiratory failure, disseminated intravascular coagulation, severe coagulation disorders, microthrombotic formation, pulmonary thromboembolism, and myocardial infarction.

The LCR, NLR, and D-dimer values can be used as markers to reduce COVID-19 morbidity and mortality. In addition, using these parameters may be necessary to monitor patients more closely, change the method of treatment, and move them to the intensive care unit. The most significant advantages of the present study were that, at least to the best of our knowledge, the number of study subjects (n = 2,000) was markedly higher than that in all previous studies (Yang *et al.*, 2020; Bal *et al.*, 2021; Salciccioli *et al.*, 2015; Jimeno *et al.*, 2021; Yan *et al.*, 2020) conducted, and strong statistical analyses could be made.

However, certain limitations of the present study should be mentioned. The present study was a single-center retrospective study. Thus, the possibility of overlooked asymptomatic or mild patients, the inability to monitor changes in the parameters in these patients due to the single blood result of patients whose clinical exacerbation rapidly exacerbated, the uncertainty of the effect of patient comorbidity and treatment on the blood results, and the improvement in some patients at the time of hospitalization were limitations of the study. Another limitation was that the pediatric age group was not included in our study because the number of patients was not sufficient.

In conclusion, the low LCR and NLR are biomarkers associated with the presence, prognosis, and mortality of COVID-19. The low LCR is more useful in this regard. These parameters can be used in clinical monitoring to reduce morbidity and mortality rates. Patients with a low LCR or high NLR should be admitted to an isolation ward with respiratory monitoring and supportive care. Supportive treatment can be applied early using these markers for a better prognosis and reduced mortality and cost. The ease of measurement and low cost of these markers can increase their usability. Despite the large number of patients herein, prospective studies with more extensive patient series are required to more clearly reveal the association between the LCR, NLR, and D-dimer values with the presence of COVID-19 and disease severity.

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