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Relationship Between D-dimer/Lymphocyte Ratio and CURB-65 Scores in COVID-19 Pneumonia Prognosis and Mortality

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Abstract

Objective: To determine effective factors for predicting mortality and prognosis of COVID-19 pneumonia. We aimed to evaluate the efficacy of D-dimer, lymphocyte count, D-dimer/lymphocyte ratio (DLR), and confusion, uremia, respiratory rate, blood pressure, age ≥65 years (CURB-65) score in predicting 30-day mortality and prognosis.

Materials and Methods: We retrospectively analyzed 248 patients with COVID-19 pneumonia presenting. Age, gender, complaint, history of chronic disease, reverse transcription polymerase chain reaction results, D-dimer levels, lymphocyte count, DLR, and CURB-65 scores were recorded, and receiver operating characteristic curve analysis was performed to predict 30-day mortality.

Results: It was found that the CURB-65 score, D-dimer level, lymphocyte count, and DLR value at the time of admission were significant predictors of mortality within 30 days ($p<0.001$). In the receiver operating characteristic analysis for the diagnostic value of the CURB-65 score and DLR for 30-day mortality, the area under the curve value for the CURB-65 and DLR were 0.862 and 0.82, respectively ($p<0.001$). The median CURB-65, D-dimer, lymphocyte count, and DLR of patients who required intensive care unit were significantly different ($p<0.001$).

Conclusion: In patients with COVID-19 pneumonia, CURB-65 score, DLR level, and disease severity are correlated at the time of presentation to the emergency department. Our study is the first to compare the correlation. We found that a positive correlation between biomarkers may be helpful for assessing mortality and prognosis and predicting the need for ICU in patients with COVID-19 pneumonia.

Keywords: CURB-65, COVID-19, D-dimer/lymphocyte ratio, emergency medicine

Introduction

COVID-19 is a disease with multisystem involvement that develops as a result of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection. COVID-19 can be asymptomatic or cause mild, moderate, or severe clinical pictures [1]. Although pulmonary involvement with fever, cough, and dyspnea is at the forefront of COVID-19 clinics, cardiac, gastrointestinal, hepatic, renal, neurologic, olfactory, gustatory, ocular, cutaneous, and hematologic symptoms may also occur due to the involvement of extrapulmonary structures [2]. Most hospitalizations and mortality rates are attributable to lung involvement and associated respiratory failure [3]. COVID-19 is diagnosed by reverse transcription polymerase chain reaction (RT-PCR) of SARS-CoV-2 [4].

The lack of biomarkers for the clinical presentation and prognosis of patients makes it difficult to predict mortality and intensive care unit (ICU) needs.

Laboratory parameters have been studied to predict poor prognosis in patients infected with SARS-CoV-2. Increased D-dimer, cardiac troponins, white blood cell, lactate, lactate dehydrogenase, creatinine phosphokinase, and creatinine

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levels, decreased lymphocyte and platelet counts, and low albumin levels are associated with poor prognosis [5-7].

There are various scoring systems used to predict prognosis in pneumonia. The confusion, uremia, respiratory rate, blood pressure, age ≥65 years (CURB-65) score is a scoring system used to predict 30-day mortality in patients with pneumonia. There are publications reporting that the CURB-65 score is reliable in predicting mortality due to COVID-19 pneumonia [8].

In addition, SARS-CoV-2 infection is associated with coagulopathy, which increases mortality and is characterized by elevated levels of procoagulant factors, such as fibrinogen and predominantly D-dimer [9,10]. In patients with severe SARS-CoV-2 infection, lymphopenia with hypocytokinemia is also noted [11].

Accordingly, the aim of this study was to investigate the efficacy of D-dimer level, lymphocyte count, D-dimer/lymphocyte ratio (DLR), and CURB-65 score in predicting mortality and prognosis in SARS-CoV-2 PCR-positive patients with pneumonia diagnosed by computed thoracic tomography.

Materials and Methods

This study was conducted Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2020/05-02, date: 27.05.2020). Data were obtained from the hospital information management system and patient files. We conducted this study by retrospectively analyzing the data of patients presenting to the adult emergency department of a tertiary hospital with COVID-19 symptoms between April and September 2020.

During the study period, 5988 patients were admitted. Patients with incomplete study data, patients under 18 years of age, patients with negative RT-PCR tests, patients without COVID-19 pneumonia, and pregnant patients were excluded from the study. RT-PCR was positive in 612 non-pregnant patients aged 18 years and older for whom complete study data were available. A total of 248 patients with a positive RT-PCR test and pneumonia were included in the study.

A standardized study data entry form was created, and demographic information (age, gender), date of admission to the emergency department, vital signs (respiratory rate, Glasgow Coma score (GCS), systolic blood pressure, diastolic blood pressure, oxygen saturation (SPO_2), presence/absence of confusion, admission complaints, chronic diseases, thoracic computed tomography imaging and radiology specialist interpretation, laboratory values (BUN, D-dimer, lymphocyte count, DLR), RT-PCR results, and CURB-65 scores were recorded from patients' files. The patient's outcome status in the emergency department (discharge, hospitalization in the ward, ICU hospitalization, and exitus) was added to the data. In addition, the need for ICU admission within 1 week and mortality within 30 days were monitored. After the study was completed, the data in the study forms were saved in an electronic format for statistical analysis.

Statistical Analysis

IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY: USA. Released 2012) was used for statistical analysis. Mean ± standard deviation or median values and an interquartile range (IQR) of 25-75% were used to express descriptive statistics, whereas categorical variables were explained as numbers and percentages (%). The Kolmogorov-Smirnov test was used to determine the normality of data distribution. Levene's test was used to determine whether the assumption of homogeneity of variances was satisfied. The significance of the difference between the groups in terms of continuous numerical variables for which parametric test statistical assumptions were met was examined using Student's t-test, while the significance of the difference in terms of continuous numerical variables for which parametric test statistical assumptions were not met was evaluated using the Mann-Whitney U test. Receiver operating characteristic curves were drawn to investigate the diagnostic values of CURB-65, D-dimer, lymphocyte count, DLR, and 30-day mortality. Logistic regression analysis was performed to identify factors affecting mortality. Results were presented at a 95% confidence interval. $P<0.05$ was considered statistically significant.

Results

A total of 248 patients were included in the study. The median age of the patients was 63 (IQR 51-74) years. While 125 (50.4%) of the patients were male, and 150 (60.5%) had a history of comorbidity. The most common comorbidities were hypertension (33.9%) and diabetes mellitus (27.8%). The most common symptoms and signs were shortness of breath in 101 (40.7%) and cough in 97 (39.1%) patients, respectively. One-hundred and eighty three (73.8%) of the patients were hospitalized in the ward, while 24 (9.68%) were in the ICU. The clinical and demographic data of the patients are shown in Table 1.

The median CURB-65 score was 1.0 (IQR 0-2.0), the mean D-dimer level was 2.27±7.50 µg/mL, the mean lymphocyte count was 2.05±8.61 10^3/mL, and the mean DLR was 2.47±6.03 (Table 2).

Differences in CURB-65 score, D-dimer level, lymphocyte count, and DLR with 30-day mortality. As a result, the median CURB-65 score, D-dimer level, lymphocyte count, and DLR of patients who died within 30 days were statistically significantly different from those in whom mortality did not develop ($p<0.001$) (Table 3).

In the receiver operating characteristic (ROC) analysis of the diagnostic value of the variables for 30-day mortality, the area under the curve (AUC) of CURB-65 was 0.862 ($p<0.001$) and the AUC of DLR was 0.820 ($p<0.001$).

The sensitivity of CURB-65 for 30-day mortality was 76.6% and specificity 82.1%, the sensitivity of D-dimer was 70.2% and specificity 70.1%, the sensitivity of lymphocyte count was 61.7% and specificity 10.4%, and the sensitivity of DLR was 74.5% and specificity 74.6% (Table 4).

There was a difference in the median CURB-65, D-dimer, lymphocyte count, and DLR of hospitalized patients in the ward with the need for ICU admission within 1 week. As a result, the median CURB-65, D-dimer, lymphocyte count, and DLR of patients who required ICU were significantly different ($p<0.001$) (Table 5).

Table 1. Clinical and demographic data

		n	%
Gender	**Female**	123	49.6
	Male	125	50.4
Chronic diseases		50	60.5
Asthma		15	6
COPD		12	4.8
DM		69	27.8
Hypertension		84	33.9
Neurological disorders		15	6
Cardiovascular diseases		35	14.1
CRF		8	3.2
Others		8	3.2
Symptoms			
Confusion		12	4.8
Shortness of breath		101	40.7
Cough		97	39.1
Fever		53	21.4
Fatigue		46	18.5
Nausea-vomiting		9	3.6
Headache		10	4.0
Joint pain		11	4.4
Others		39	18
Emergency service outcome	Outpatient follow-up	39	15.7
	Service admission	183	73.8
	Intensive care hospitalization	24	9.7
	Exitus	2	0.8
Intensive care hospitalization within a week		66	26.6
30 day mortality		47	19

COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CRF: Chronic renal failure

Logistic regression analysis was performed using the variables of age, sex, and comorbidity history, which may affect 30-day mortality. Age [exp. beta=1.051 (95% confidence interval 1.026-1.077), $p<0.001$] was found to be an effective factor for the diagnosis of 30-day mortality.

In the analysis performed to investigate whether there was a relationship between the patients' CURB-65, D-dimer, lymphocyte count, and DLR ratios, a significant positive correlation was found between DLR and CURB-65 and D-dimer, respectively [($p<0.001$, $r=0.409$), ($p<0.001$, $r=0.878$)], and a negative correlation was also detected with the lymphocyte count ($p<0.05$, $r=-0.587$) (Table 6).

Table 2. Analysis of variables

Age, median (IQR 25-75)	63 (51-74)
GCS, median (IQR 25-75)	15 (15-15)
Respiration rate/minute median (IQR 25-75)	17 (14-21)
BUN-mg/dL mean ± standard deviation	21.56±16.32
DBP-mmHg, median (IQR 25-75)	80 (70-84)
SBP-mmHg, median (IQR 25-75)	130 (120-140)
SPO_2-mmHg (mean ± standard deviation)	93.22±5.65
CURB-65, median (IQR 25-75)	1 (0-2)
D-Dimer-mcg/mL, mean ± standard deviation	2.27±7.50
Lymphocyte count-mcL, (mean ± standard deviation)	2.05±8.61
DLR, (mean ± standard deviation)	2.47±6.03

GCS: Glasgow Coma scale, BUN: Blood urea nitrogen, SPO_2: Oxygen saturation, DLR: D-dimer/lymphocyte ratio, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age≥65 years

Table 3. Thirty-day mortality analysis of variables

	30-Day mortality	n	Median (IQR: 25-75)	p*
CURB-65	No	201	1.0 (0-1.0)	**<0.001**
	Yes	47	2.0 (2.0-2.0)	
	Total	248	1.0 (0-2.0)	
D-dimer - mcg/mL	No	201	0.67 (0.38-1.08)	**<0.001**
	Yes	47	1.97 (0.87-4.46)	
	Total	248	0.77 (0.42-1.35)	
Lymphocyte mcL	No	201	1.40 (0.95-1.95)	**<0.001**
	Yes	47	0.80 (0.52-1.25)	
	Total	248	1.31 (0.80-1.87)	
DLR	No	201	0.44 (0.24-0.87)	**<0.001**
	Yes	47	2.41 (0.82-6.21)	
	Total	248	0.54 (0.29-1.57)	

*Mann-Whitney U test, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years,

n: Frequency DLR: D-dimer/lymphocyte ratio, IQR: Interquartile range

Table 4. ROC analysis for the 30-day mortality prediction of variables

AUC (95% CI)	p	Risk factor	Cut-off	Sensitivity %	Specificity %
0.862 (0.812-0.912)	<0.001	CURB-65	1.5	76.6	82.1
			2.5	23.4	98.0
			3.5	12.8	100.0
0.780 (0.708-0.852)	<0.001	D-dimer	0.865	76.6	62.2
			0.945	70.2	70.1
			1.150	66.0	77.1
0.270 (0.186-0.354)	<0.001	Lymphocyte	0.675	61.7	10.4
			1.095	31.9	29.9
			1.195	27.7	34.3
0.820 (0.758-0.882)	<0.001	DLR	0.701	85.1	69.2
			0.830	74.5	74.6
			0.901	72.3	75.6

AUC: Area under the curve, CI: Confidence interval, DLR: D-Dimer/Lymphocyte ratio, ROC: Receiver operating characteristic, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years

Table 5. Analysis of variables from service to ICU admission in a week

	ICU need	n	Median (IQR: 25-75)	p
CURB-65	No	141	1.0 (0-1.0)	**<0.001**
	Yes	42	2.0 (1.0-2.0)	
	Total	183	1.0 (0-1.0)	
D-dimer - mcg/mL	No	141	0.63 (0.37-0.96)	**<0.001**
	Yes	42	1.62 (0.91-3.84)	
	Total	183	0.75 (0.42-1.19)	
Lymphocyte - mcL	No	141	1.48 (1.03-2.07)	**<0.001**
	Yes	42	0.84 (0.60-1.61)	
	Total	183	1.33 (0.85-1.95)	
DLR	No	141	0.37 (0.22-0.75)	**<0.001**
	Yes	42	1.70 (0.85-6.31)	
	Total	183	0.50 (0.28-1.16)	

n: Frequency; DLR: D-dimer/lymphocyte ratio; ICU: Intensive care unit, IQR: Interquartile range, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years

Table 6. CURB-65, d-dimer, lymphocyte count and DLR correlation analysis

			CURB-65	D-dimer	Lymphocyte count	DLR
Spearman's rho	CURB-65	r	1.000	0.420*	-0.217*	0.409*
		p		**<0,001**	0.001	**<0.001**
	D-dimer	r	0.420*	1.000	-0.189*	0.878*
		p	**<0,001**	-	0.003	**<0.001**
	Lymphocyte count	r	-0.217*	-0.189*	1.000	-0.587*
		p	0.001	0.003	-	**<0.001**
	DLR	r	0.409*	0.878*	-0.587*	1.000
		p	**<0.001**	**<0.001**	**<0.001**	-

*Spearman's correlation analysis,

DLR: D-dimer/lymphocyte ratio, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥65 years

Discussion

Rapid and reliable biomarkers and scoring systems are critical for prognosis and mortality in patients with COVID-19 pneumonia in emergency departments. Unfortunately, we do not have practical usable and easy-to-perform tests in this regard. In this retrospective study, we aimed to investigate whether CURB-65 levels, D-dimer levels, lymphocyte counts, and DLR, which can be easily performed at every hospital, can be used to predict the prognosis and mortality of patients with COVID-19 pneumonia.

The CURB-65 is a scoring system used to predict 30-day mortality in patients with pneumonia, classify patients as low, intermediate, and high risk, and decide on outpatient follow-up, hospital ward, or ICU hospitalization. The higher the CURB-65 score, the higher the mortality rate. In a study by Satici et al. [12] a CURB-65 score of 2 or higher was found to be discriminative in predicting 30-day mortality. Işler and Kaya [13] found that the CURB-65 score was an independent predictor of mortality in patients with COVID-19 pneumonia.

Nguyen et al. [14] reported that the CURB-65 score was strongly associated with poor prognosis. However, in the same study, it was stated that it would not be reliable in determining the outpatient follow-up of patients with COVID-19 pneumonia because 36 of 171 patients with CURB-65 score 0-1, which is considered a low-risk group, had a poor prognosis. In a multicenter retrospective cohort evaluating severity indices in COVID-19 pneumonia, the AUC of the CURB-65 score in predicting mortality was found to be 0.825 and it was stated that the CURB-65 score was suboptimal in predicting the need for intensive care [15].

In our study, the median CURB-65 score of the patients was 1.0. On the other hand, the median CURB-65 score of patients who developed mortality within 30 days was 2.0. In the ROC analysis of the diagnostic value of the CURB-65 score for 30-day mortality, the AUC was 0.862. In the study by Zhou et al. [16] it is seen that patients with a CURB-65 score of 2 had the highest number of deaths. In our study, the CURB-65 score of patients who required ICU within a week and had a fatal course was 2. Patients with COVID-19 pneumonia who had a CURB-65 score of 2 were likely to need ICU but were ignored and hospitalized in the wards. This should be taken into consideration in pneumonia that may develop in possible COVID-19 outbreaks because, in community-acquired pneumonia, a CURB-65 value of 3-5 for the need for ICU increases the mortality risk (15-40%) [17,18]. In our study, unlike CAP, we believe that a CURB-65 value of 2 is more appropriate for the need for ICU in COVID-19 pneumonia.

According to many studies, a high D-dimer level is a reliable coagulation parameter for predicting poor prognosis and mortality. D-dimer levels were found to be higher in patients requiring ICU admission [19,20]. In our study, a correlation was found between high D-dimer levels and 30-day mortality. In the ROC analysis of the diagnostic value of D-dimer level for 30-day mortality, the AUC was 0.780. Among the patients who were hospitalized in the ward, D-dimer levels were higher in those who needed ICU within one week. In our study, the need for ICU significantly increased in patients with D-dimer levels above 1.62 mg/L. In addition, the D-dimer level was found to be 1.97 mg/L for 30-day mortality.

The relationship between the need for ICU within 1 week and the development of one-month mortality with D-dimer levels was found to be consistent with the literature. In a case-control study by Yao et al. [21] it was reported that D-dimer was the only parameter that was significantly correlated with mortality in multivariate analysis, and a D-dimer level of >2.14 mg/L was significant. Therefore, elevated D-dimer levels at presentation may indicate poor prognosis. Hachim et al. [22] stated that COVID-19 patients with D-dimer levels of >1.5 mg/dL, urea levels of >6.5 mmol/L, and troponin levels of >13.5 ng/mL need to be admitted to the ICU due to the risk of a more mortal course.

In many studies, lymphopenia has been associated with the severity of COVID-19, accepted as a prognostic factor in the course of the disease, and shown to be a mortality marker [23,24]. In a study by Tan et al. [25] the lymphocyte count was found to be associated with mortality; the lymphocyte count and the ratio of patients who died were significantly lower than surviving patients. The cutoff lymphocyte count was found to be ≤0.65 10^9/L [25]. In a meta-analysis, the presence of lymphopenia at presentation was associated with severe disease progression and death [26]. A meta-analysis by Huang and Pranata [27] found a relationship between low lymphocyte counts and COVID-19 severity, ARDS development, and mortality.

The peripheral blood lymphocyte counts and subsets have been shown to be significantly lower than normal in the majority of COVID-19 patients, especially in severe cases with previously reported and confirmed SARS [28]. In our study, a statistically significant relationship was found between low lymphocyte counts and 30-day mortality. The cutoff lymphocyte count was found to be ≤0.80 10^9/L. Similar to other studies, there was a relationship between lymphopenia presence and mortality.

DLR can be used to evaluate both the effects of SARS-CoV-2 infection on immune cells and the coagulopathy caused by it [10,29]. In addition, DLR can be a risk factor indicator in the mortality of COVID-19 patients. Peng et al. [30] found that the combination of DLR was more effective against COVID-19-induced mortality than considering D-dimer or lymphocyte values individually.

Similarly, our study found that DLR was more effective in predicting the need for ICU admission within 1 week and 1 month in patients with COVID-19 pneumonia than D-dimer elevation and low lymphocyte levels.

These findings suggest that DLR can also be used as a marker to determine the need for ICU within 1 week.

Study Limitations

This study has several limitations. First, the findings were obtained from a limited number of patients admitted to our emergency department. Second, this was a single-center, retrospective study.

Conclusion

We believe that lymphocyte count, CURB-65 score, D-dimer level, and DLR, which are among the parameters studied to predict the prognosis of COVID-19 pneumonia, can be used to predict the need for ICU hospitalization within 1 week and 30-day mortality. We believe that the use of these values, which can be easily obtained at every hospital, can reduce mortality and determine the need for ICU admission. In this regard, studies with higher participation rates should be conducted.

Ethics

Ethics Committee Approval: This study was conducted Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2020/05-02, date: 27.05.2020).

Informed Consent: A retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.S., Y.İ., H.K., Concept: M.Y., M.O.A., Design: B.S., M.O.A., Data Collection or Processing: B.S., Y.İ., H.K., Analysis or Interpretation: B.S., H.K., M.Y., M.O.A., Literature Search: B.S., Y.İ., M.O.A., Writing: B.S., Y.İ., H.K., M.Y., M.O.A.

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