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Combined Use of D-dimer and NLR as a Prognostic Index in COVID-19

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What is known on this subject?

The reported mortality rate of coronavirus disease-2019 (COVID-19) patients has a wide range with the estimated rate of the World Health Organization being 3.4% in the world. Due to the heterogeneous clinical course, it is difficult to predict prognosis early on hospital admission, which can rapidly progress leading to high mortality.

What this study adds?

In this cross-sectional study, we aimed to investigate the combined use of D-dimer and neutrophil-to-lymphocyte ratio as coagulation and inflammation parameters, respectively, rather than a single parameter to predict mortality in COVID-19 patients.

ABSTRACT

Objective: We aimed to investigate the combined use of D-dimer and neutrophil-to-lymphocyte ratio (NLR) as a prognostic index-coronavirus disease (PRI-COVID) in COVID-19 patients to predict mortality.

Material and Methods: We included 152 COVID-19 patients in our cross-sectional study. The cut-off value of D-dimer to predict mortality was 1.07 µg/mL with a sensitivity of 68% and specificity of 80% [area under curve (AUC) ± SE: 0.752±0.05; positive predictive value (PPV) 39.5%, and negative predictive value (NPV) 92.7%; p<0.001]. Meanwhile, at a cut-off value of 3.83, the sensitivity and specificity of NLR in predicting mortality were 92% and 48.8%, respectively (AUC ± SE: 0.730±0.05; PPV: 26.1%; NPV: 96.9%; p<0.001). We categorized patients as low, moderate, and high risk using the PRI-COVID model (low risk: <1.07 D-dimer and <3.83 NLR; moderate risk: >1.07 D-dimer or >3.83 NLR; high risk: >1.07 D-dimer and NLR >3.83). High-risk PRI-COVID was associated with 6.37 times increased risk of death compared with the low/moderate risk group.

Results: Combined use of coagulation and inflammation parameters might can be associated with mortality.

Conclusion: Our results suggest that PRI-COVID is easy to assess and useful in predicting both 30-day and overall survival in patients with COVID-19.

Keywords: SARS-CoV-2 infection, D-dimer, fatal outcome, inflammation

Introduction

The reported mortality rate of coronavirus disease-2019 (COVID-19) patients has a wide range with the estimated rate of the World Health Organization (WHO) being 3.4% in the world (1). Due to the heterogeneous clinical course, it is difficult to predict the prognosis early on hospital admission, which can rapidly progress leading to high mortality. There is urgently needed for indexes consisting of clinical and laboratory parameters to predict the fatal progression of disease. As such, risk stratification would be critically lifesaving in

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terms of providing timely and successful management of this deadly disease. Although several parameters have been proposed as prognostic factors, limited data are available to evaluate the association between coagulation parameters and inflammation markers on mortality in COVID-19. Recently, increased D-dimer levels have been recognized in severe ill patients besides several biochemical and clinical features (2). Further, retrospective data and pooled analysis have shown that D-dimer has the potential to predict mortality (3,4). Despite available data indicating the prognostic role of D-dimer, a combined model rather than a single parameter would be more helpful.

Neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), a systemic inflammatory response (SIR) indicator, has been demonstrated to be a useful predictor of COVID-19. Elevated NLR results in a clinically increased level of NEUs and decreased level of LYMs, and has been proposed as a new biomarker for systemic inflammation. Recent studies showed that higher levels were associated with the severity of disease and could be an independent predictor of mortality in hospitalized patients (5,6). More effort needs to be given in analyzing the panel, including the prediction probability of NLR and D-dimer, which will provide a more personalized approach for the COVID-19 patients.

In this cross-sectional study, we aimed to investigate the combined use of D-dimer and NLR as coagulation and inflammation parameters, respectively, rather than a single parameter to predict mortality in COVID-19 patients.

Material and Methods

Study Design and Patients

In this single-center cross-sectional and observational study, 152 moderate to severe consecutively hospitalized patients (mean age 58.2±13.7 years; 64 female, 88 male) in University of Health Sciences Turkey, Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital (tertiary care hospital in Turkey) with confirmed infection of severe acute respiratory syndrome coronavirus-2 by real-time reverse transcriptase-polymerase chainreaction of nasal and pharyngeal swab samples between 15 April 2020 and 1 December 2020 included. Patients' severity was defined according to WHO clinical management guidance of COVID-19 (7). The criterion for severe COVID-19 were percutaneous oxygen saturation (SpO_2) of lower than 90%, respiratory rates ≥30/min, the need for use of high-flow nasal cannula, or non-invasive mechanical ventilation using the biolevel positive airway pressure mode due to hypoxemia. Patients not reaching the criteria for severe COVID-19 and having pulmonary involvement associated with COVID-19 were considered non-severe. Patients who required mechanical ventilation and/or transfer to the intensive care unit for high-flow oxygen support were classified as critical. Classification according to computed tomography was conducted, evaluating the abnormalities as percent (%). Patients divided into groups mild (<%10), moderate (10-70%), severe (70%) (8).

Methods

This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval no: 2284). An informed consent form was signed by each subject included in the study.

NLR and D-dimer have been analyzed as markers of inflammation and coagulation, respectively. The combined model containing NLR and D-dimer has been named the predictive index for COVID-19 (PRI-COVID), and its role in predicting mortality has been investigated. Epidemiological and at the time of hospital admission and clinical data obtained from medical records, patient charts, and databases have been prospectively recorded. D-dimer levels were detected by Siemens BCSXP. All biochemical analyzes of the patients were performed in the biochemistry laboratory using the Beckman Coulter AU2700 device and Sysmex XT4000i devices. The D-dimer levels and hemogram blood samples were measured on admission to the hospital with the latex agglutination method.

Disease outcomes were interpreted as disease survivors and non-survivors obtained from computer-based national records. Receiver operator curve (ROC) and Cox regression analysis have been used to analyze critical values (optimal cut-off values associated with Youden index) and prognostic roles of combined use of D-dimer and NLR independent of other confounders.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) 13.0 for Windows 20 (IBM SPSS Inc., Chicago, IL). Categorical variables are presented as n (%), and normally distributed values are presented as mean ± standard deviation (SD). Multivariate Cox regression models were applied to determine independent risk factors predicting mortality. ROC analysis was applied to define the minimal optimal D-dimer and NLR level that predicted death, and cut-off value was evaluated according to the Youden index method. A statistical relative measure of Cox regression models was evaluated using the Akaike information criterion

and ROC curve analysis. Kaplan-Meier survival curves and log-rank tests were used to compare the time to death between those with elevated D-dimer and NLR levels and those without. The results are presented as hazard ratios (HRs) with 95% confidence interval. A p value <0.05 was considered significant.

Results

One hundred fifty-two hospitalized COVID-19 patients (mean age 58.2±13.7 years; 64 female, 88 male) were included in this study. There were more male patients in the cohort with similar mortality results to the females (p=0.40). Twenty (13%) patients were intubated. The mean length of stay was 9 (2-60) days. Sixteen deaths have occurred (10.5%) in 30-day period. Twenty-five patients (16.5%) have died in overall, while 127 (83.5%) patients survived. Median follow-up was 77 day (min 2-max 307 day). A hundred and four (68%) patients classified as severe and 48 (32%) patients considered as non-severe had mortality rates of 22% and 14%, respectively (p=0.25). Demographical features and clinical factors of survivors and non-survivors are shown in Table 1. The mean ± SD age of non-survived cases was 67.9±12.8 years, which is older than that of survived patients (<0.001). The most common pre-existing comorbidities were hypertension (HT) (41%), diabetes mellitus (30%), ischemic heart disease (21%), chronic obstructive pulmonary disease (COPD) (17%), and asthma (16.5%) in our cohort. Prevalence of comorbidities including COPD (HR: 2.74; p=0.019), HT (HR: 2.41; p=0.031), malignancy (HR: 4.83; p<0.001) was higher in non-survivors. A higher comorbidity index (HR: 1.54; p<0.001) was detected in non-survivors (Table 1).

Decreased resting arterial SpO_2 (HR: 0.92; p<0.001), abnormal radiologic pathology higher than 50% (HR: 3.47;

Table 1. Demographical features of patients with COVID-19

Variables	All population	Survival		Univariable regression			
		Survivors	Non-survivors	HR	95% CI		p
	n=152	n=127	n=25		Lower	Upper	
Age, years	58.2±13.7	56.3±13	67.9±12.8	1.07	1.03	1.10	<0.001*
Gender, n(%)							
Female	64 (42.1)	55 (43.3)	9 (36.0)	ref	-	-	-
Male	88 (57.9)	72 (56.7)	16 (64.0)	1.41	0.62	3.20	0.408
Weight, kg	81.4±17.1	83.3±17.2	71.8±13.2	0.96	0.94	0.99	0.003*
Height, cm	169±8.6	169.6±8.4	165.8±9.1	0.96	0.91	1.00	0.066
BMI, kg/m^2	28.4±5.2	28.8±5.3	26.2±4	0.91	0.83	0.99	0.022*
Obesity, n (%)	60 (39.5)	54 (42.5)	6 (24.0)	0.45	0.18	1.12	0.084
Smoke, n (%)							
Non-smoker	78 (51.7)	68 (54.0)	10 (40.0)	ref	-	-	-
Current smoker	15 (9.9)	12 (9.5)	3 (12.0)	1.60	0.44	5.82	0.475
Exsmoker	58 (38.4)	46 (36.5)	12 (48.0)	1.78	0.77	4.12	0.178
Smoke, pack/year	30 (0-150)	30 (0-150)	40 (0-125)	1.01	1.00	1.02	0.070
Comorbidity index	1 (0-7)	1 (0-6)	2 (0-7)	1.54	1.27	1.85	<0.001*
Asthma	25 (16.4)	21 (16.5)	4 (16.0)	0.95	0.32	2.76	0.920
COPD	26 (17.1)	18 (14.2)	8 (32.0)	2.74	1.18	6.34	0.019*
DM	46 (30.3)	36 (28.3)	10 (40.0)	1.57	0.70	3.49	0.270
HT	62 (40.8)	47 (37.0)	15 (60.0)	2.41	1.08	5.36	0.031*
IHD	32 (21.1)	26 (20.5)	6 (24.0)	1.12	0.45	2.82	0.803
CHF	14 (9.2)	10 (7.9)	4 (16.0)	1.83	0.63	5.34	0.266
CRF	4 (2.6)	3 (2.4)	1 (4.0)	1.37	0.19	10.13	0.758
Malignancy	15 (9.9)	8 (6.3)	7 (28.0)	4.83	2.00	11.63	<0.001*

*Numerical variables were shown as mean ± standard deviation or median (minimum-maximum). Categorical variables were expressed as numbers and percentages.*p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, IHD: Ischemic heart disease, CHF: Congestive heart failure, CRF: Chronic renal failure, BMI: Body mass index*

p=0.016), the need for intubation (HR: 24.39; p<0.001), and severe cases according to risk score (HR: 3.09; p=0.017) were detected as clinical risk factors associated with increased risk of mortality (Table 2). Furthermore, increased D-dimer (HR: 1.38; p<0.001) or NLR levels (HR: 1.09; p<0.001) and decreased LYM count (HR: 0.13; p<0.001) have been shown as laboratory abnormalities associated with increased risk of death in univariate analyzes (Table 3). The mean D-dimer and NLR levels across all patients with COVID-19 were 0.7 (0.2-6.2) and 4.5 (0.7-39.5), respectively.

Mortality-associated risk factors included the cox-regression model (Table 4). In the multivariate analysis, decreased SpO_2 (HR: 0.90; p<0.001), increased creatinine (HR: 3.11; p=0.005), and increased D-dimer (HR: 1.34; p=0.037) have been detected as independent predictors of mortality in model I (Table 4). When the laboratory parameters were included in model II (Table 4), decreased SpO_2 (HR: 0.92; p<0.001), increased D-dimer (HR:1.35; p=0.029) and NLR (HR: 1.07; p=0.005) have continued to be independent predictors of mortality. In model III (Table 4), D-dimer and NLR combination was tested to predict mortality with the pre-tested cut-off value in the ROC analysis. The optimum cut-off value of D-dimer to predict mortality was 1.07 µg/mL with a sensitivity of 68% and a specificity of 80% [area under curve (AUC) ± SE: 0.752±0.05]. ROC curve analysis for using NLR to predict mortality indicated an optimal cut-off >3.83 with a sensitivity of 92% and specificity of 48.8% [AUC ± SE: 0.730±0.05; positive predictive value (PPV): %26.1; negative predictive value: 96.9%; p<0.001]. We investigated the predictive accuracy of the combined model including

D-dimer and NLR. We were able to categorize patients as low, moderate, and high risk using the PRI-COVID model (low risk: <1.07 D-dimer and <3.83 NLR; moderate risk: >1.07 D-dimer or >3.83 NLR; high risk: >1.07 D-dimer and NLR >3.83). Model III was the best model to predict mortality independently (Figure 1). Patients with high-risk PRI-COVID had 6.37 times (HR: 6.37; p<0.001) increased risk of 30-day mortality and 5.82 times (HR: 5.82; p<0.001) increased risk of overall mortality when compared to low/moderate PRI-COVID patients (Figure 2).

Table 2. Clinical features with the comparisons between survivors and non-survivors

Variables	All population	Survival		Univariable regression			p
		Survivors	Non-survivors		95% CI		
	n=152	n=127	n=25	HR	Lower	Upper	
BMR, x10^3	1.4 (0.5-2.8)	1.5 (0.5-2.8)	1.3 (0.5-1.9)	1.00	1.00	1.00	0.088
ER, x10^3	1.8 (0.6-3.4)	1.8 (0.6-3.4)	1640 (0.6-2.3)	1.00	1.00	1.00	0.463
BT							
Mild	55 (36.2)	50 (39.4)	5 (20.0)	ref	-	-	-
Moderate	32 (21.1)	28 (22.0)	4 (16.0)	1.58	0.42	5.88	0.498
Severe	65 (42.8)	49 (38.6)	16 (64.0)	3.47	1.27	9.51	0.016*
Saturation	89.3±7.2	90.3±6	84.3±10.1	0.92	0.88	0.95	<0.001*
Clinical weight 1							
Non-severe	48 (31.6)	42 (33.1)	6 (24.0)	ref	-	-	-
Severe	42 (27.6)	41 (32.3)	1 (4.0)	0.19	0.02	1.61	0.129
Critical	62 (40.8)	44 (34.6)	18 (72.0)	3.09	1.22	7.82	0.017*
Clinical weight 2							
Non-severe	48 (31.6)	42 (33.1)	6 (24.0)	ref	-	-	-
Severe	104 (68.4)	85 (66.9)	19 (76.0)	1.71	0.68	4.30	0.250
ICU intubated	20 (13.2)	4 (3.1)	16 (64.0)	24.39	10.59	56.17	<0.001*
Length of stay in hospital	9 (2-60)	9 (2-45)	10 (2-60)	1.02	0.99	1.06	0.196

*Numerical variables were shown as mean ± standard deviation or median (min-max). Categorical variables were expressed as numbers and percentages. *p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, CIT: Complaint initiation time, BMR: Basal met rate, ER: Energy requirement, ICU: Intensive care unit*

Discussion

The mortality rate in our cohort was 16.5% and was consistent with the results of previous studies (9,10). However, depending on the heterogeneous nature of the disease, the characteristics of the patients included, and the sample size, it appears that mortality rates can be in a wide range.

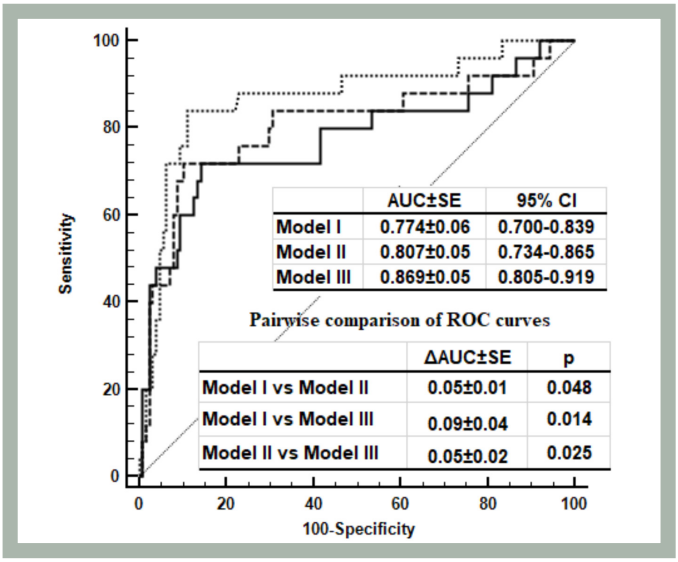

Figure 1. Receiver operator characteristic curve for D-dimer and NLR to predict deaths (comparisons of models)

NLR: Neutrophil-to-lymphocyte ratio, AUC: Area under curve, CI: Confidence interval

Excessive inflammation and platelet activation play a significant role in the development of prothrombotic states, which might play a role in the increased mortality of COVID-19. There is urgently needed for clinical and laboratory predictors of the progression of the disease toward severe and fatal forms. In earlier reports, several potential predictors have been revealed but none of the distinctive panels, rather than a single parameter, have emerged to be used sufficiently to predict prognosis. In this study, we showed that the combined model of D-dimer and NLR, called "PRI-COVID", can be used as a risk assessment index to more precisely predict prognosis with favorable sensitivity and specificity, rather than a single parameter in COVID-19.

In the retrospective study of Wang et al. (11), 119 middle-aged patients were included and having a comorbidity was exclusion criteria. Univariate and multivariate regression models were performed, and pri-covid was found to be a statistically significant predictor of mortality in COVID-19. Furthermore, the need for a larger study sample was emphasized in that study.

D-dimer has not been previously identified as a specific marker for viral pneumonia (12). However, increased D-dimer levels reported in COVID-19 patients in a wide range of 3.75 to 68% may simply reflect both thrombotic and fibrinolytic activities (13,14). Although different cut-off values were used in retrospective cohorts, non-survivors had significantly higher D-dimer levels (14,15,16), similar to the results of our study. D-dimer has been suggested as a potential marker for predicting in-hospital mortality, with an increased risk of

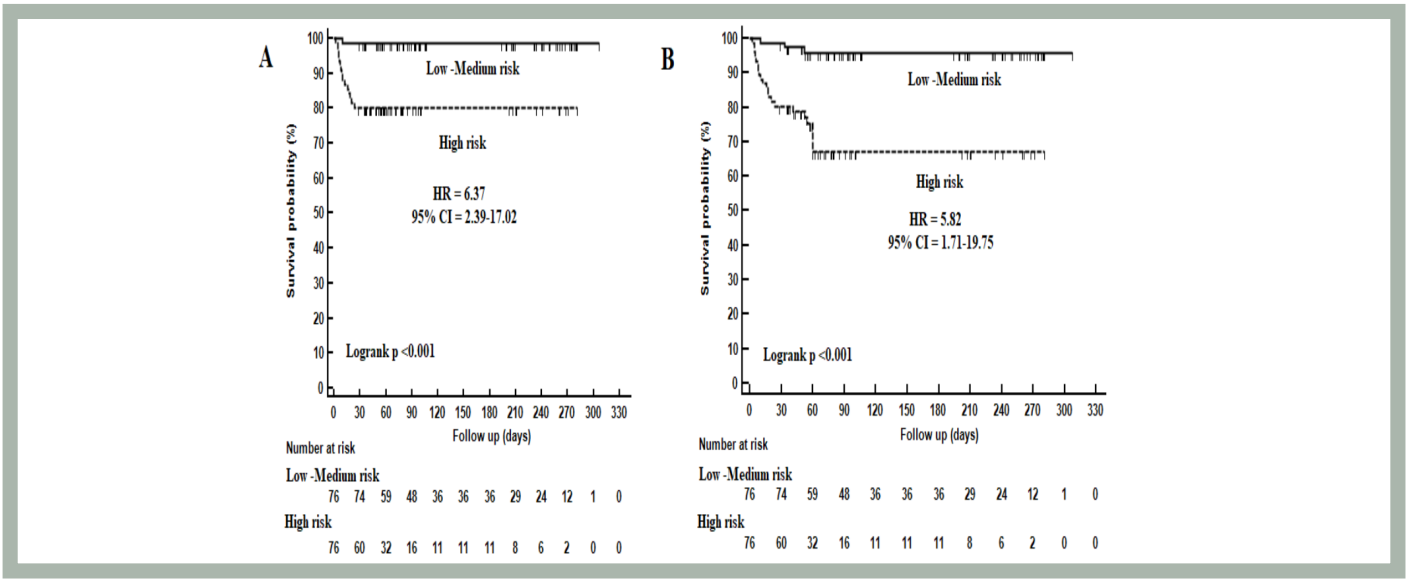

Figure 2. Kaplan-Meier survival curves for PRI-COVID (combined index with D-dimer and NLR) on admission. Comparisons of 30-day (A) and overall (B) mortality risk according to the PRI-COVID risk index

NLR: Neutrophil-to-lymphocyte ratio, HR: Hazard ratio, CI: Confidence interval, PRI-COVID: Predictive index for coronavirus disease

death even with D-dimer higher than 0.5 mg/L (adjusted HR: 1.75) in a large-scale study (17). Another retrospective study investigated optimal cut-off values for baseline D-dimer levels in 343 COVID-19 patients, which could also predict in-hospital mortality. D-dimer can predict in-hospital mortality with a cut-off value of 2.0 µg/mL, favorable sensitivity and specificity results (4) (92.3% and 83.3%, respectively), D-dimer might have an impact in predicting in-hospital mortality in patients with COVID-19 based on most retrospective analyses despite high heterogeneity and several limitations in the studies (3,4,18,19). There is no conclusive evidence that D-dimer plays an exact role in-hospital as well as in overall mortality, independent of other confounding factors, and that its use with markers of inflammation may lead to predict outcomes more precisely. In this cross-sectional study, our analysis indicates that D-dimer levels at admission can be useful for predicting both 30-day mortality and overall mortality. Increased D-dimer is associated with 1.38 times increased

Table 3. Laboratory results with the comparisons between survivors and non-survivors

Variables	All population	Survival		Univariable regression			
		Survivors	Non-survivors	HR	95% CI		p
	n=152	n=127	n=25		Lower	Upper	
CRP	66 (0.3-336)	57.3 (0.3-336)	102 (3.4-224)	1.00	1.00	1.01	0.119
D-dimer	0.7 (0.2-6.2)	0.6 (0.2-5.8)	1.3 (0.3-6.2)	1.38	1.10	1.72	<0.001*
Lymphocyte	1.2 (0.2-7.2)	1.3 (0.2-7.2)	0.7 (0.2-2.2)	0.13	0.05	0.38	<0.001*
LYM, %	17.4 (2.4-50.6)	18.7(3-50.6)	10 (2.4-46.6)	0.91	0.86	0.96	<0.001*
MPV	9.8±1	9.8±1	10.1±1.3	1.41	0.95	2.08	0.085
PDW	13.3±2.7	13.2±2.7	13.6±2.9	1.09	0.94	1.27	0.268
PLT	219.5 (97-487)	218 (97-487)	234 (103-476)	1.00	1.00	1.01	0.312
ALT	26 (3-616)	26 (3-616)	23 (3-184)	1.00	0.99	1.01	0.888
AST	34 (12-220)	33.5 (12-220)	35 (13-166)	1.01	1.00	1.02	0.277
Albumin	37.9±4.4	38.4±4.1	35.2±4.9	0.87	0.79	0.94	0.001*
e-GFR	92 (17-126)	93 (26-126)	76.5 (17-110)	0.97	0.96	0.99	<0.001*
CK	75 (15-2018)	73 (15-2018)	77 (25-1053)	1.00	1.00	1.00	0.152
Glucose	127 (63-724)	127 (63-516)	136 (73-724)	1.00	0.99	1.01	0.096
Urea	34 (12-124)	32 (12-109)	48 (15-124)	1.03	1.02	1.05	<0.001*
Creatinine	0.9 (0.4-3.3)	0.9 (0.5-2.3)	0.9 (0.4-3.3)	4.07	2.29	7.24	<0.001*
LDH	345 (128-1374)	327 (128-849)	386 (224-1374)	1.03	1.01	1.05	<0.001*
Uric acid	4.8 (2.2-13)	4.7 (2.3-13)	5.3 (2.2-12.5)	1.22	1.01	1.47	0.038*
Haematocrit	38.5±5	39±4.5	36±6.4	0.90	0.83	0.97	0.008*
Hemoglobin	12.9±1.8	13.1±1.6	11.9±2.3	0.72	0.58	0.90	0.004*
Troponin	2.7 (0-112.5)	2.3 (0-40)	13.9 (0-112.5)	1.03	1.02	1.05	<0.001*
Ferritin	321.9 (16-2000)	316.7 (16-2000)	492 (39-1500)	1.05	1.01	1.10	0.028*
Fibrinogen	547.5±181	548.7±184.6	541.0±163.8	1.00	1.00	1.00	0.955
Procalcitonin	0.07 (0.02-8.07)	0.06 (0.02-8.07)	0.19 (0.03-7.51)	1.27	1.03	1.57	0.023*
proBNP	129 (3-15432)	113 (3-12953)	2298.5 (81-15432)	1.04	1.01	1.08	<0.001*
PT (%)	96.1±15.4	97±14.6	90.9±19.3	0.98	0.96	1.00	0.081
aPTT	27.1±6.6	27.1±6.4	26.7±7.9	1.00	0.94	1.07	0.940
NLR	4.5 (0.7-39.5)	4.1 (0.7-30.2)	7.8 (0.9-39.5)	1.09	1.05	1.13	<0.001*

*Numerical variables were shown as mean ± standard deviation or median (minimum-maximum). Categorical variables were expressed as numbers and percentages.*p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, CRP: C-reactive protein, PLT: Platelet, CK: Creatine kinase, LDH: Lactate dehydrogenase, PT: Prothrombine time, NLR: Neutrophil-to-lymphocyte ratio, LYM: Lymphocyte, MPV: Mean platelet volume, PDW: Platelet distribution width, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, e-GFR: Estimated glomerular filtration rate, PT: Prothrombin time, aPTT: Activated partial thromboplastin time*

risk of death with the optimum cut-off value of 1.07 µg/mL, which was reported in several variability in previous studies (14,15,16,17). It seems that when a D-dimer is used as a single marker, its contribution to predict mortality may be limited. Indeed, in a retrospective cohort study by Ye et al. (9), the peak value of the D-dimer.

Rather than baseline D-dimer value was shown to be associated with prognosis. Therefore, an easily applicable index model, as suggested in our study, could provide a potential field for more precise risk assessment.

The mechanisms underlying the increased D-dimer levels in COVID-19 are not clearly defined. Recent evidence indicates that sepsis-induced coagulopathy, evidence of disseminated intravascular coagulation (DIC) are not the only mechanisms responsible for increased D-dimer levels associated with severe COVID-19 patients (20). Importantly, increased pro-inflammatory cytokines have been shown in severe cases. Excessive inflammation and platelet activation might have crosstalk to the augmented effect of the procoagulant state in COVID-19 (21) while playing a significant role in the development of prothrombotic states, which result in increased mortality. Additionally, autopsy results have supported the fact that excessive NEU infiltration in capillaries leading to NEU extracellular traps can contribute to the thrombotic process (22). Increased inflammation and increased thrombosis might be associated (23). Furthermore, hypoxia also plays a role in the triggered procoagulant activity through the releasing of several cytokines. Based on increasing evidence, COVID-19 infection results in a prothrombotic state with an increased risk of venous thromboembolism (24). The anti-inflammatory effect of low-molecular-weight heparin (LMWH) has been reported in COVID-19 infection, which is characterized by the disregulation of the immune system response with increased pro-inflammatory. Furthermore, LMWH has recently been advised as a part of treatment care in hospitalized COVID-19 patients recently (2,14). However, the effect of systemic anticoagulation therapy on the reduced risk of mortality has not been well evaluated. It seems that hypercoagulability is in close association with an inflammatory response in COVID-19 and might behave as an additive effect on the disease outcomes.

White blood cell count, NEU-to-LYM-NLR, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio are indicators of the SIR that were investigated as useful predictors for poor outcomes of viral pneumonia in several studies previously (25,26). NLR has been suggested as a potential inflammatory marker in severe cases, but there is insufficient data on how efficiently can be used to predict mortality (5,10,27). The critical value of NLR was 3.83 in our cohort, which is reported in a wide range in previous studies

Table 4. **Independent risk factors predicting mortality**

Variables	Multivariable Cox regression			
	HR	95% CI		p
		Lower	Upper	
Model I				
Oxygen saturation	0.90	0.86	0.94	<0.001*
Creatinine	3.11	1.41	6.89	0.005*
D-dimer	1.34	1.02	1.76	0.037*
	-2 Log likelihood: 178.7; AIC: 239			
Model II				
Oxygen saturation	0.92	0.88	0.97	<0.001*
D-dimer	1.35	1.03	1.73	0.029*
NLR	1.07	1.02	1.11	0.005*
	-2 Log likelihood: 204.5; AIC: 224			
Model III				
Oxygen saturation	0.92	0.88	0.96	<0.001*
D-dimer and NLR combination				
Low-medium risk	Ref			
High risk	5.82	1.71	19.75	0.005*
	-2 Log likelihood: 204.2; AIC: 202			

**p<0.05 indicates statistical significance. HR: Hazard ratio, CI: Confidence interval, AIC: Akaike information criterion, NLR: Neutrophil-to-lymphocyte ratio*

(10,16,27) and slightly lower than the previously reported data (16,24) NLR has been detected as an independent risk factor for mortality in our cohort as in previous studies (5,6). Recently, each unit of NLR increase has been associated with a gradually increased risk of in-hospital mortality, especially in males (6). However, several factors such as body mass index, physical activity, smoking, alcohol consumption, and gender that may have an impact on NLR values limit the reliability of its use alone (28). Our results suggested that initial NLR by itself cannot have enough specificity to predict mortality with the poor PPV, which was also mentioned by Ye et al. (9).

NLR is an easy-to-obtain, inexpensive feasible marker reflecting the inflammatory response and might have an adjunct predictive power of D-dimer for patients with COVID-19. Thus, a combined model of D-dimer and NLR can more precisely determine the high risk of mortality.

Different assessment models, mostly based on machine learning models, have been developed for the best prediction analysis of mortality until now (29,30,31). Except for one recently published study (29), none of them included D-dimer although C-reactive protein, lactic dehydrogenase, and LYM count have been included as predictors.

Study Limitations

The limitation of our study was the single-center design, on the other hand, there were features to perform a stronger study. Our study sample consists of a population having comorbidities, so our results became more determinative. Furthermore, the larger sample size and the need for more studies on PRI-COVID emphasize the contributive features of our study.

Conclusion

Our prognostic model consisting of NLR and D-dimer could objectively predict critical cases more determinatively than single use of these factors to predict mortality in COVID-19 patients. These inexpensive and easily accessible biomarkers would provide the best model and would have significancy in predicting the mortality of COVID-19 patients with high differentiation ability. When we used a combined model including D-dimer and NLR, we could increase both specificity and sensitivity of predicting prognosis in this deadly disease. Thus, D-dimer and NLR have been used as a prognostic index named “PRI-COVID” to classify patients at hospital admission and this enables early detection of potential critical patients.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval no: 2284).

Informed Consent: An informed consent form was signed by each subject included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.P.Y., S.B., Concept: B.P.Y., D.G.H., C.A., Design: B.P.Y., C.A., Data Collection or Processing: B.P.Y., D.G.H., S.B., Analysis or Interpretation: B.P.Y., D.G.H., C.A., Literature Search: B.P.Y., D.G.H., S.B., Writing: B.P.Y., C.A.

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