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Short Communication

Biomarkers for predicting COVID-19 mortality: A study at Sulianti Saroso Infectious Disease Hospital, Indonesia

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Abstract

The high transmissibility and mortality rates of the COVID-19 pandemic pose significant challenges. Patients can deteriorate rapidly, making it crucial to identify laboratory biomarkers for high-risk individuals. The aim of this study was to evaluate the predictive value of various laboratory parameters, including C-reactive protein (CRP), D-dimer, ferritin, neutrophil-to-lymphocyte ratio (NLR), prothrombin time (PT), and procalcitonin (PCT), in predicting COVID-19 mortality. A retrospective cohort study was conducted at Sulianti Saroso Infectious Disease Hospital, where COVID-19 patients were categorized into survivors and non-survivors. The Mann-Whitney test was used to assess group differences, while receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of each biomarker, with Youden's index (J) determining optimal cut-off values. Kaplan-Meier analysis was used to compare median survival times, and Cox regression assessed hazard rates and the relationship between biomarkers and mortality. A total of 1,598 patients were analyzed, the majority of whom were admitted with oxygen saturation levels >95% and classified as having mild to moderate disease severity. Among them, 216 patients died, resulting in a mortality rate of 13.52%. Significant variations in mortality rates were observed along the survival functions for NLR, ferritin, D-dimer, CRP, and PCT (p<0.001). The survival curves for these biomarkers demonstrated distinct trends across tertiles over time. Among hematological markers, NLR was significantly associated with mortality (p<0.001), with a 1.5–2.2% increased risk per unit increase. Biochemical markers (complete blood count) proved to be more effective than hematological parameters (NLR, ferritin, PT, D-dimer, CRP, PCT) when evaluating individual prognostic performance. Bivariate analysis of CRP, D-dimer, ferritin, NLR, PT, and PCT between survivors and non-survivors showed significant differences. Notably, NLR and PCT were highly relevant for predicting disease prognosis and mortality, with sensitivity and specificity values exceeding 80%.

Keywords: COVID-19, survival, biomarker, mortality, Sulianti Saroso Hospital

Introduction

The global health emergency triggered by coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused significant resource

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shortages, leading to the collapse of healthcare systems globally, with particularly severe impacts [1-4]. The infection process of SARS-CoV-2 involves binding of the virus's spike protein to the angiotensin-converting enzyme 2 (ACE-2) receptor [5], which triggers excessive production of proinflammatory cytokines, leading to a cytokine storm. Dysregulation of the immune response may result in acute respiratory distress syndrome (ARDS) and multiple organ dysfunction, contributing to the severity of COVID-19 [6,7]. As COVID-19 progresses, various immunological and metabolic reactions produce biomarkers that change over time and reflect the severity of the disease [8-10].

Several biomarkers associated with the severity and mortality of COVID-19 have been identified [4,11]. Lymphocyte count and procalcitonin (PCT) (bacterial co-infection markers); D-dimer, fibrinogen, and platelet count (coagulation-related biomarkers); C-reactive protein (CRP), creatine kinase (CK), ferritin, and interleukins (IL-1b, IL-6, IL-8), and neutrophil-to-lymphocyte ratio (NLR); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (liver enzymes); and lactate dehydrogenase (LDH) and troponin (markers of cardiac distress) have been associated with COVID-19 severity and mortality [6,10,12-16]. These markers can help guide disease progression and treatment strategies. Nevertheless, additional studies are needed to confirm their diagnostic accuracy in broader patient populations and to determine the precise thresholds for these biomarkers in individuals with severe clinical presentations. In addition, complete blood count (CBC) offers valuable information on coagulation status, inflammation, and infection as biochemical markers [6,17]. Given their clinical significance, hematological markers and follow-up for all patients with moderate or severe COVID-19 are routinely assessed upon hospital admission. The aim of this study was to assess the predictive values of biochemical and hematological biomarkers on outcomes of patients with severe COVID-19 in Indonesia.

Methods

Study design and patients

A retrospective study was conducted at Sulianti Saroso Infectious Disease Hospital in Jakarta, Indonesia, the national reference hospital for infectious diseases. Between March 2, 2020, and December 31, 2022, the hospital reported 3,928 COVID-19-positive patients from Jakarta and the surrounding areas. The study included all COVID-19 patients admitted to the intensive care unit (ICU) of Sulianti Saroso Infectious Disease Hospital from March 2020 to December 2022. During this period, 1,598 patients were hospitalized. The study population consisted of adults who tested positive for SARS-CoV-2 through real-time polymerase chain reaction (RT-PCR) testing. Patients with incomplete data or those who were pregnant were excluded.

Study variables

COVID-19, as defined by the Indonesian Ministry of Health regulation [18], was characterized by cases that were confirmed through the nucleic acid amplification method using RT-PCR testing, in accordance with the guidelines established by the World Health Organization [19]. Patients who were diagnosed by physicians based on clinical symptoms and confirmed positive through RT-PCR testing were recorded in both electronic medical records and the national COVID-19 surveillance system in Indonesia.

In this study, various possible risk factors were assessed and collected, including variables categorized into demographic, clinical, symptomatic, comorbidity-related, vaccination status, and laboratory parameters. Demographic variables included age, sex, and citizenship. Clinical variables covered the severity of illness, ward type, oxygen saturation, respiratory aid, and length of hospital stay. Symptomatic variables encompassed a range of symptoms such as fever, cough, cold, sore throat, numbness, anosmia, diarrhea, nausea, vomiting, muscle pain, fatigue, headache, and shortness of breath. Comorbidity-related variables included conditions like obesity, tuberculosis, HIV, asthma, cardiovascular diseases, stroke, diabetes mellitus, and hypertension, along with the number of comorbidities. Vaccination status was also recorded, detailing whether individuals received one dose, two doses, a booster, or were not vaccinated for COVID-19. Laboratory parameters included hematologic and biochemical markers such as NLR, ferritin levels, prothrombin time (PT), D-dimer, CRP, and PCT levels.

The outcomes of this study were categorized into two groups: COVID-19 patients who were reported to have survived/recovered and those who did not survive (non-survivors). Surviving COVID-19 patients were classified as those who were discharged from the hospital after two consecutive PCR-negative test results, as per established clinical protocol [18]. Non-surviving patients were identified based on cases that were managed in accordance with the standardized protocol for handling deceased individuals with COVID-19, as implemented in institutions equipped with forensic medicine and medicolegal specialists.

Data sources

The target population was obtained from the surveillance of hospitalized COVID-19 patients. Demographic data were collected. Clinical symptoms and manifestations were recorded at the initial presentation when the patient was admitted to the emergency department (ED). Subsequently, laboratory parameters were extracted from the EMR. Additional data from the EMR included disease severity, ward of care, initial oxygen therapy, length of stay, comorbid disease, and patient outcomes. The information was extracted from documentation by the attending physician. The laboratory biomarker parameters analyzed were the first test results upon patient admission, using reference values based on hospital standards. These results were validated by a clinical pathology specialist and documented in the EMR by a laboratory analyst. Ward of care in this study was defined as last ward in the hospitalization period. Oxygen therapy refers to the initial therapy given upon patient admission, while the length of stay was calculated from admission to discharge.

Data collections

Data collection was conducted using a case report form (CRF). Clinical symptoms such as fever, cough, runny nose, sore throat, headache, myalgia, diarrhea, nausea-vomiting, and shortness of breath were evaluated and recorded. Comorbidities such as heart disease, hypertension, diabetes, asthma, human immunodeficiency virus (HIV) infection, tuberculosis infection, obesity, and stroke were also evaluated. Hematological markers such as CRP, D-dimer, ferritin, NLR, PT, and PCT were measured. All laboratory biomarkers were measured and recorded on the admission date. Demographic variables such as age and sex, as well as the risk factors of infection, such as contact and travel history, were collected by direct interview.

Data analysis

After data entry, coding was performed to ensure consistency, followed by a data cleaning process to maintain accuracy and reliability. Laboratory parameters were assessed based on the reference values used at Sulianti Saroso Infectious Disease Hospital. The median and interquartile range (Q1-Q3) were used to summarize variables. Absolute and relative frequencies served as a summary of categorical factors. The Mann-Whitney test for bivariate analysis, Kaplan-Meier analysis to compare median survival values, and the association between biomarkers and mortality were assessed using Cox regression to obtain hazard ratios ($\alpha<0.05$). A log-rank test was used to evaluate the global differences between survival curves, ensuring the absence of crossing patterns ($p<0.001$). Significant biomarkers identified using the Wald test were included in the multivariable models ($p<0.05$). These models were developed using the Cox regression method to further analyze the relationship between biomarkers and mortality. We have performed Cox regression to control for confounding variables. All database variables were used to create a model made up of biological markers. A time-dependent receiver operating characteristic (ROC) curve analysis was used to individually assess the performance of each explanatory biomarker. Each biomarker's area under the curve (AUC), sensitivity, and specificity were estimated, and an ideal cut-off point was determined using the Youden index [20].

Results

Patients' characteristics

A total of 1,598 patients were analyzed, most of whom were admitted with an oxygen saturation level of >95% and classified as having mild to moderate disease severity (**Table 1**). Among all

patients, 216 died, resulting in a mortality rate of 13.52%. Survivors were more likely to have mild to moderate disease severity, while non-survivors predominantly presented with severe or critical illness (**Table 1**). A higher proportion of non-survivors required ICU admission and ventilatory support, whereas most survivors were managed in general hospital wards. Oxygen saturation levels above 95% were more common in survivors, while non-survivors frequently had lower levels. Comorbidities were more prevalent among non-survivors, particularly diabetes mellitus, hypertension, and cardiovascular diseases. Additionally, non-survivors were less likely to have received a full COVID-19 vaccination. Regarding symptoms, shortness of breath, fatigue, headache, and gastrointestinal symptoms were more frequently reported among non-survivors (**Table 1**).

Factors associated with mortality

Our data indicated many factors associated with mortality among COVID-19 patients (**Table 1**). Male sex was associated with increased mortality (p=0.002), as was older age (p<0.001). Indonesian citizenship was also more common among non-survivors (p=0.042). A history of contact with confirmed COVID-19 cases was linked to higher mortality (p=0.037). Shortness of breath (p<0.001), fatigue (p=0.008), headache (p=0.016), diarrhea (p=0.025), and nausea/vomiting (p=0.041) were more frequently observed in non-survivors (**Table 1**).

Severe or critical disease was strongly associated with mortality (p<0.001), as was ICU admission (p<0.001) and the need for ventilatory support (p<0.001) (**Table 1**). Non-survivors were more likely to have oxygen saturation levels below 90% (p<0.001) and a hospital stay of more than ten days (p=0.019). The presence of comorbidities was significantly associated with mortality, particularly diabetes mellitus (p=0.005), hypertension (p=0.003), and cardiovascular diseases (p=0.007). Having two or more comorbidities further increased the risk of death (p<0.001). Additionally, non-survivors were less likely to have received a full COVID-19 vaccination (p=0.027) (**Table 1**).

Some hematologic parameters were also associated with mortality (**Table 1**). An elevated NLR (NLR>9.47) was associated with mortality (p<0.001). Ferritin levels frequently exceeded the normal range of 40–200 µg/mL in non-survivors (p<0.001). Prolonged PT (PT>15.00 seconds) was also linked to increased mortality (p<0.001). Higher D-dimer levels (>0.50 µg/mL) were observed in non-survivors (p<0.001). Elevated CRP (CRP>5.00 mg/dL) was significantly associated with mortality (p<0.001), reflecting an advanced inflammatory response. Similarly, increased PCT (PCT>0.50 µg/mL) was more frequent among non-survivors (p<0.001), indicating a greater likelihood of severe systemic infection (**Table 1**).

Table 1. Comparison of the characteristics between survivors and non-survivors of COVID-19 (n=1,598)

Variable demography	Total (n=1,598), n (%)	Survivors (n=1,382), n (%)	Non-survivors (n=216), n (%)	p-value [a]
Age (median, IQR)	47 (35–59)	45 (33.75–57.00)	58 (51.00–66.00)	<0.001
Sex				
Male	751	80 (37.04)	671 (48.55)	0.002**
Female	847	136 (62.96)	711 (51.45)	
Citizenship				
Foreigner	38	1 (0.46)	37 (2.68)	0.047*
Indonesian	1,560	215 (99.54)	1,345 (97.32)	
Risk transmission				
Contact history				
None	1,099	907 (65.6)	192 (88.9)	<0.001**
Yes	499	475 (34.4)	24 (11.1)	
Travelling history				
None	1,449	1,250 (91.6)	199 (98.0)	0.002**
Yes	119	115 (8.4)	4 (2.0)	
Symptoms				
Fever				
None	879	771 (55.8)	108 (50.0)	0.129
Yes	719	611 (44.2)	108 (50.0)	
Cough				
None	294	249 (18.0)	45 (20.8)	0.369
Yes	1,304	1,133 (82.0)	171 (79.2)	

Variable demography	Total (n=1,598), n (%)	Survivors (n=1,382), n (%)	Non-survivors (n=216), n (%)	*p*-value [a]
Cold				
None	1,290	1,087 (78.7)	203 (94.0)	<0.001**
Yes	308	295 (21.3)	13 (6.0)	
Sore throat				
None	1,418	1,220 (88.3)	198 (91.7)	0.177
Yes	180	162 (11.7)	18 (8.3)	
Numbness				
None	1,556	1,344 (97.3)	212 (98.1)	0.590
Yes	42	38 (2.7)	4 (1.9)	
Anosmia				
None	1,398	1,189 (86.0)	209 (96.8)	<0.001**
Yes	200	193 (14.0)	7 (3.2)	
Diarrhea				
None	1,525	1,312 (94.9)	213 (98.6)	0.026*
Yes	73	70 (5.1)	3 (1.4)	
Nausea-vomiting				
None	1,252	1,083 (78.4)	169 (78.2)	1.000
Yes	346	299 (21.6)	47 (21.8)	
Muscle pain				
None	1,512	1,302 (94.2)	210 (97.2)	0.097
Yes	86	80 (5.8)	6 (2.8)	
Fatigue				
None	1,271	1,108 (80.2)	163 (75.5)	0.132
Yes	327	274 (19.8)	53 (24.5)	
Headache				
None	1,267	1,076 (77.9)	191 (88.4)	0.001**
Yes	331	306 (22.1)	25 (11.6)	
Shortness of breath				
None	918	870 (63.0)	48 (22.2)	<0.001**
Yes	680	512 (37.0)	168 (77.8)	
Clinical Severity				
Mild/moderate	1,283	1,223 (88.5)	60 (27.8)	<0.001**
Severe/critical	315	159 (11.5)	156 (72.2)	
Ward type				
Hospitalization ward	1,138	1,097 (79.4)	41 (19.0)	Ref
ICU non-ventilator	261	205 (14.8)	56 (25.9)	<0.001**
ICU ventilator	199	80 (5.8)	119 (55.1)	<0.001**
Ward type				
Non-ventilator	1,399	97 (44.91)	1,302 (94.21)	<0.001**
Ventilator	199	119 (55.09)	80 (5.79)	
Oxygen saturation				
>95%	1,575	199 (92.1)	1,376 (99.6)	Ref
90–95%	12	7 (3.2)	5 (0.4)	<0.001**
<90%	11	10 (4.6)	1 (0.1)	<0.001**
Respiratory aid				
Without oxygen	1,538	1,341 (97.0)	197 (91.2)	Ref
Nasal cannula/	28	27 (2.0)	1 (0.5)	0.145
Oxygen face mask/high-flow nasal cannula/ventilator	32	14 (1.0)	18 (8.3)	<0.001**
Length of stay				
1–10 days	740	618 (44.7)	122 (56.5)	0.002**
>10 days	858	764 (55.3)	94 (43.5)	
Comorbidities				
Obesity				
None	1,597	1,381 (99.9)	216 (100.0)	1.000
Yes	1	1 (0.1)	0 (0.0)	
Tuberculosis				
None	1,595	1,380 (99.9)	215 (99.5)	0.873
Yes	3	2 (0.1)	1 (0.5)	
HIV infection				
None	1,594	1,379 (99.8)	215 (99.5)	1.000
Yes	4	3 (0.2)	1 (0.5)	
Asthma				
None	1,597	1,382 (100.0)	215 (99.5)	0.286
Yes	1	0 (0.0)	1 (0.5)	
Cardiovascular disease				

Variable demography	Total (n=1,598), n (%)	Survivors (n=1,382), n (%)	Non-survivors (n=216), n (%)	*p*-value [a]
None	1,596	1,381 (99.9)	215 (99.5)	0.635
Yes	2	1 (0.1)	1 (0.5)	
Stroke				
None	1,594	1,378 (99.7)	216 (100.0)	0.953
Yes	4	4 (0.3)	0 (0.0%)	
Diabetes mellitus				
None	1,566	1,362 (98.6)	204 (94.4)	<0.001**
Yes	32	20 (1.4)	12 (5.6)	
Hypertension				
None	1,564	1,360 (98.4)	204 (94.4)	<0.001**
Yes	34	22 (1.6)	12 (5.6)	
Amount comorbidities				
None	1,546	199 (92.13)	1,347 (97.47)	Ref
1	27	6 (2.78)	21 (1.52)	0.262
≥2	25	11 (5.09)	14 (1.01)	0.001*
Comorbidities				
None	1,546	1,347 (97.5)	199 (92.1)	<0.001**
Yes	52	35 (2.5)	17 (7.9)	
COVID-19 vaccine				
2-dose/booster	40	38 (2.7)	2 (0.9)	Ref
1-dose	8	8 (0.6)	0 (0.0)	0.518
None	1,550	1,336 (96.7)	214 (99.1%)	0.109
COVID-19 vaccine				
2-dose/booster	40	38 (2.7)	2 (0.9)	0.173
1-dose/none	1,558	1,344 (97.3)	214 (99.1)	
Hematologic parameters				
Neutrophil-to-lymphocyte ratio (median, IQR)	3.24 (1.94–6.15)	2.86 (1.85–4.56)	11.32 (6.92–18.20)	<0.001**
≤9.47	1,345	1,263 (91.4)	82 (38.0)	<0.001**
>9.47	253	119 (8.6)	134 (62.0)	
Ferritin				
Ferritin (median, IQR)	386 (132.75–1202.75)	299 (110.00–834.00)	1918.50 (1081.50–2001.00)	<0.001**
40–200	392	388 (28.1)	4 (1.9)	<0.001**
<40 or >200	1,206	994 (71.9)	212 (98.1)	
Prothrombin time				
Prothrombin time (median, IQR)	10.70 (10.10–11.40)	10.60 (10.10–11.30)	11.00 (10.40–11.90)	<0.001**
11.00-15.00	577	475 (34.4)	102 (47.2)	<0.001**
<11.00 or >15.00	1,021	907 (65.6)	114 (52.8)	
D-dimer				
D-dimer (median, IQR)	0.60 (0.30–1.20)	0.50 (0.30–1.00)	1.65 (0.80–4.18)	<0.001**
≥0.50	995	798 (57.7)	197 (91.2)	<0.001**
<0.50	603	584 (42.3)	19 (8.8)	
C-reactive protein				
C-reactive protein (median, IQR)	17.32 (4.0–66.5)	12.22 (4.00–46.82)	103.82 (53.57–161.86)	<0.001**
≥5.00	1,108	899 (65.1)	209 (96.8)	<0.001**
<5.00	490	483 (34.9)	7 (3.2)	
Procalcitonin				
Procalcitonin (median, IQR)	0.05 (0.02–0.14)	0.04 (0.02–0.09)	0.39 (0.16–1.78)	<0.001**
≥0.50	177	78 (5.6)	99 (45.8)	<0.001**
<0.50	1,421	1,304 (94.4)	117 (54.2)	

HIV: human immunodeficiency virus; ICU: intensive care unit; IQR: interquartile range; Ref: reference group

* Statistically significant at $p<0.05$

** Statistically significant at $p<0.01$

Hematological biomarkers' performance to predict mortality in COVID-19 patients

A Cox proportional hazards regression model with backward selection was used to identify significant hematological markers associated with COVID-19 mortality. Both crude hazard ratios (CHR) and adjusted hazard ratios (AHR) with 95% confidence intervals (CI) were reported (**Table 2**). Among the hematological markers, the NLR was the strongest predictor of COVID-19

mortality, showing a significant association in both crude (CHR: 2.23; 95%CI: 1.94–2.57; p<0.001) and adjusted models (AHR: 1.51; 95%CI: 1.29–1.78; p<0.001). Prothrombin time (PT) was also significantly associated with mortality (CHR: 1.16; 95%CI: 1.04–1.29; p=0.007) (**Table 2**).

Several inflammatory and coagulation markers were also significantly associated with COVID-19 mortality (**Table 2**). Ferritin was a strong predictor, with a CHR indicating a protective effect (CHR: 0.52; 95%CI: 0.46–0.58; p<0.001), although the adjusted model showed a slightly attenuated association (AHR: 0.73; 95%CI: 0.64–0.83; p<0.001). D-dimer (AHR: 0.81; 95%CI: 0.71–0.92; p=0.001), CRP (AHR: 0.76; 95%CI:0.67–0.87; p<0.001), and PCT (AHR: 0.81; 95%CI: 0.68–0.95; p=0.009) were also significantly associated with mortality, suggesting that these biomarkers play a crucial role in disease severity and patient outcomes (**Table 2**).

Table 2. Adjusted analysis of hematological markers associated with COVID-19 mortality

Biomarker	p-value [a]	Crude hazard ratio (95% confidence interval)	p-value [b]	Adjusted hazard ratio (95% confidence interval)	p-value [c]
Neutrophil-to-lymphocyte ratio	<0.001	2.23 (1.94–2.57)	<0.001	1.51 (1.29–1.78)	<0.001
Ferritin	<0.001	0.52 (0.46–0.58)	<0.001	0.73 (0.64–0.83)	<0.001
Prothrombin time	0.005	1.16 (1.04–1.29)	0.007	-	-
D-dimer	<0.001	0.61 (0.54–0.69)	<0.001	0.81 (0.71–0.92)	0.001
C-reactive protein	<0.001	0.53 (0.47–0.60)	<0.001	0.76 (0.67–0.87)	<0.001
Procalcitonin	<0.001	0.50 (0.44–0.58)	<0.001	0.81 (0.68–0.95)	0.009

The adjusted model, composed of hematological markers, was generated using Cox regression with backward selection. The most parsimonious models were selected using the Wald test (p<0.05) for a pool analysis of imputed datasets

[a] Analyzed using Log Rank Test

[b,c] Analyzed using Cox Regression test

Predictive values of biochemical and hematological markers

Kaplan-Meier survival analysis was performed to assess the impact of key biomarkers on survival outcomes in COVID-19 patients. The biomarkers analyzed included NLR, ferritin, PT, D-dimer, CRP, and PCT, each categorized into tertiles. The log-rank test showed significant global differences between survival curves for all biomarkers (p<0.001), confirming their strong association with mortality risk (**Figure 1**). Among these markers, NLR showed a clear distinction in survival, with higher tertiles associated with lower survival probabilities, indicating its strong predictive value in COVID-19 mortality. Ferritin levels also demonstrated a significant impact on survival, with elevated levels linked to worse outcomes, reflecting its role in hyperinflammation. PT was associated with increased mortality, suggesting that prolonged clotting time could contribute to poor prognosis. D-dimer, a marker of coagulation and fibrinolysis, showed significant survival differences, with higher levels indicating increased mortality risk. Similarly, CRP, a key inflammatory marker, was significantly associated with survival, where higher tertiles reflected greater systemic inflammation and worse outcomes. Finally, PCT, a biomarker of bacterial co-infection and sepsis, showed a significant survival trend, with elevated levels linked to higher mortality (**Figure 1**). Overall, these findings suggest that hematological and inflammatory markers play a crucial role in predicting COVID-19 outcomes, with higher values generally associated with worse survival probabilities.

Sensitivity and specificity of biomarkers were then tested, and the results are presented in **Table 3**. The individual performance of the biomarker was evaluated by a time-dependent ROC analysis, estimating the AUC for each biomarker, sensitivity and specificity for an optimal cut-off point according to the Youden index [21]. Our data indicated that NLR <5.86 was the strongest predictor of mortality, with the highest AUC (AUC: 0.881), sensitivity (81.5%), and specificity (82.7%) (p<0.001) (**Table 3**). PCT>0.13 also showed a high predictive value (AUC: 0.889), with a sensitivity of 82.9% and specificity of 81.3% (p<0.001). Ferritin>582.50 was highly sensitive (90.3%) but had a lower specificity (66.5%), with an AUC of 0.852 (p<0.001). CRP>38.32 demonstrated strong predictive ability (AUC: 0.829), with 84.3% sensitivity and 70.7% specificity (p<0.001). D-dimer>0.95 showed moderate predictive accuracy (AUC: 0.793), with a sensitivity of 71.3% and specificity of 74.9% (p<0.001). PT<10.85 had the weakest predictive value among

the biomarkers (AUC: 0.580), with lower sensitivity (56.9%) and specificity (58.2%) (p<0.001) (**Table 3**).

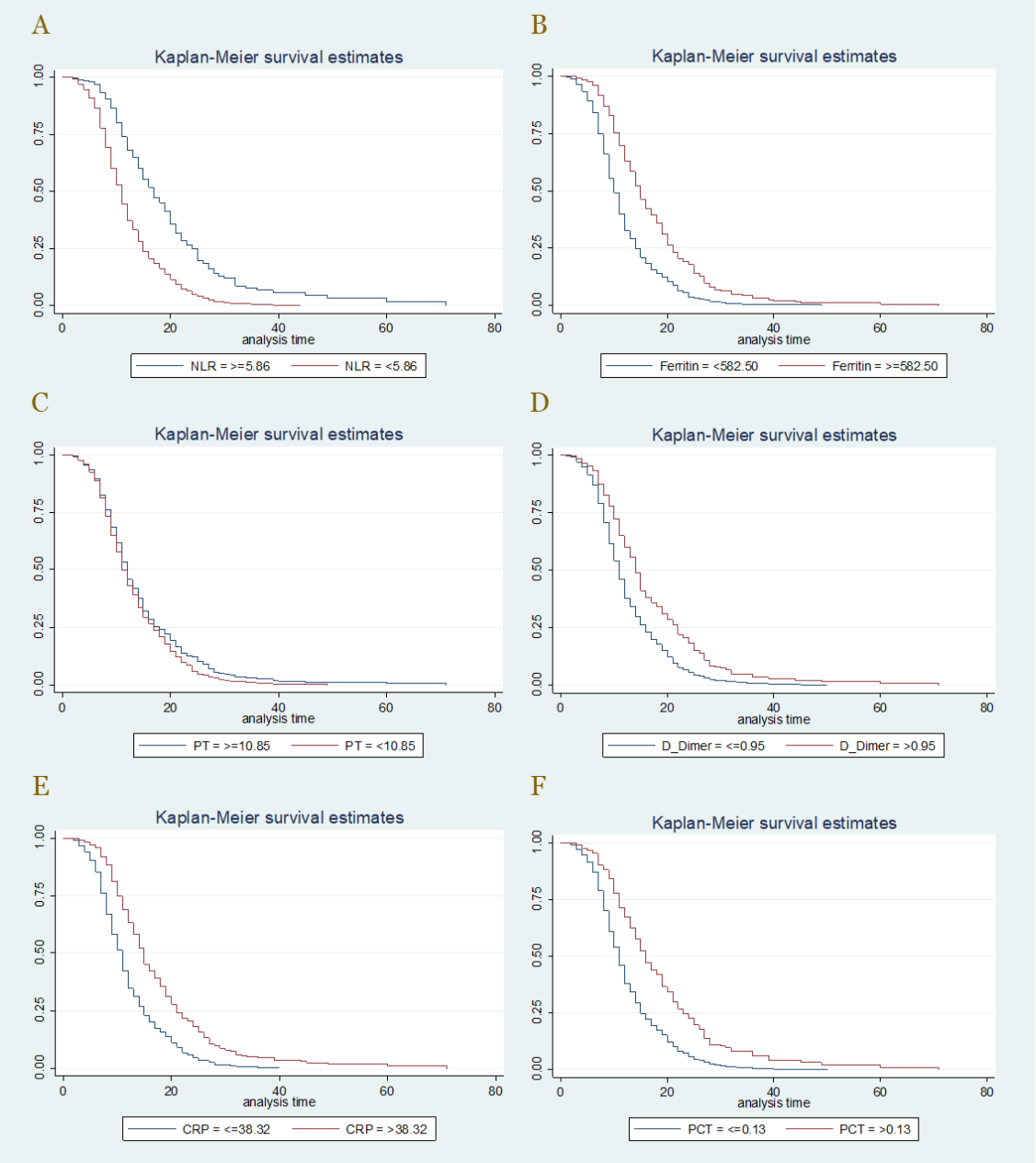

Figure 1. Kaplan-Meier survival analysis for explanatory biomarkers categorized in tertiles. Kaplan-Meier survival analysis was performed for key biomarkers, including: (A) neutrophil-to-lymphocyte ratio (NLR), (B) ferritin, (C) prothrombin time (PT), (D) D-dimer, (E) C-reactive protein (CRP), and (F) procalcitonin (PCT). The log-rank test revealed significant global differences between survival curves for all biomarkers (p<0.001), indicating their strong association with COVID-19 mortality. No crossing patterns were observed, suggesting a clear and consistent distinction in survival probabilities across tertiles.

Table 3. Sensitivity and specificity of the hematology biomarkers to predict COVID-19 mortality

Biomarker	Cut-off value	AUC	*p*-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Neutrophil-to-lymphocyte ratio	<5.86	0.881	<0.001	81.5	82.7	42.41	96.62
Ferritin	>582.50	0.852	<0.001	90.3	66.5	2.23	70.36
Prothrombin time	<10.85	0.580	<0.001	56.9	58.2	17.57	89.64
D-dimer	>0.95	0.793	<0.001	71.3	74.9	5.65	69.26
C-reactive protein	>38.32	0.829	<0.001	84.3	70.7	3.46	69.11
Procalcitonin	>0.13	0.889	<0.001	82.9	81.3	3.45	57.11

AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value

Discussion

This study aimed to determine the hematological parameters associated with mortality in hospitalized COVID-19 patients at a referral hospital prior to vaccine availability. Lower-middle-income countries often face challenges in providing adequate healthcare to COVID-19 patients [4]. Under these conditions, it is crucial to prioritize and allocate limited healthcare resources to effectively identify critical patients based on available indicators such as oxygen saturation and biomarkers [4,22]. The overall proportion of in-hospital mortality was higher than that in other countries [22-25], but consistent with Peru [26,27] and the North Coast [28]. Owing to overflowing hospitals, infected people were forced to stay at home and use non-evidence-based drugs [28,29]. Delayed hospital treatment increases the mortality rate compared to other indicators [28].

Hematological biomarkers play a crucial role in predicting COVID-19 mortality, particularly those associated with inflammation and coagulation. In this study, NLR was the strongest predictor of mortality, with significantly higher levels associated with poor survival outcomes ($p<0.001$). Elevated NLR reflects systemic inflammation and immune dysregulation, consistent with previous studies that linked high NLR values to severe COVID-19 cases and increased mortality risk [30-32]. Similarly, CRP and ferritin, both markers of inflammation, were significantly associated with worse outcomes ($p<0.001$). Overreactive immune responses mediated by IL-6 elevate CRP [6] and ferritin levels [33], which have been observed predominantly in severe or fatal COVID-19 cases [27,30,34]. The AUC for CRP in this study was 0.79, which aligns with previous reports ranging from 0.69 to 0.92, indicating moderate predictive accuracy [6,30,35]. Ferritin also demonstrated predictive value, with earlier studies reporting AUC values between 0.62 and 0.64 [17,36].

Coagulation markers such as D-dimer and PT were also significant predictors of mortality. D-dimer, which is produced during fibrin degradation, indicates the presence of thrombosis and thrombolysis [6,30,37]. This study confirmed that even survivors exhibited an elevated risk of thrombosis, emphasizing the importance of coagulation monitoring in COVID-19 management. Previous studies have suggested D-dimer cut-off values between 0.67 and 2.03 µg/ml for predicting adverse outcomes, with AUC values ranging from 0.81 to 0.889 [6,30,36]. Prolonged PT was associated with an increased risk of mortality ($p=0.007$), reflecting a higher likelihood of coagulopathy complications. Although the association between PT and mortality risk was not as strong as other markers, previous research has shown that even within normal reference ranges, prolonged PT correlates with poor outcomes [38,39].

Among infection-related biomarkers, PCT was a significant predictor of mortality ($p=0.009$), suggesting its relevance in identifying patients at risk of bacterial co-infection and sepsis. The AUC for PCT in this study was 0.81, demonstrating good sensitivity and specificity in predicting severe COVID-19 cases [4,6,39,40]. While D-dimer, CRP, and lactate dehydrogenase have been identified as the strongest predictive biomarkers, their accuracy remains limited, with none exceeding the 80% threshold for robust predictive performance.

This study has limitations, particularly related to its retrospective design and reliance on routine hospital surveillance data, which led to incomplete or unavailable data for several key variables (dates of symptom onset, hospital admission and outcome, vital signs, TB and HIV co-infection, routine laboratory results, and disease severity classification at admission). Additionally, comorbidities were often self-reported or potentially underdiagnosed, which may have contributed to underreporting and underestimation. Lastly, the findings from the hospitals reported in this study may not accurately reflect the mortality rate and risk factors associated with COVID-19-related mortality in a broader population.

Conclusion

Apart from demographic and clinical risk factors, this study highlights the critical role of hematological biomarkers in predicting COVID-19 mortality. Elevated levels of NLR, CRP, ferritin, D-dimer, PT, and PCT were significantly associated with worse survival outcomes, emphasizing their potential utility in clinical risk stratification. These findings suggest that a combination of hematological and inflammatory markers may enhance predictive models for identifying high-risk COVID-19 patients and guiding early intervention strategies.

Ethics approval

The Research Ethics Committee of Sulianti Saroso Infectious Disease Hospital approved the study protocol under approval number 26/XXXVIII.10/V/2023.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study utilized artificial intelligence (AI) tools and methodologies for manuscript writing support. AI-based language model, ChatGPT, was employed for language refinement, including grammar improvement, sentence structuring, and enhancing readability. The authors confirm that all AI-assisted processes were critically reviewed to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were made solely by the authors.

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