JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

D-Dimer, ferritin, and lactate dehydrogenase (LDH) as predictors of mortality in hospitalized COVID-19 patients

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Abstract

Introduction: Several laboratory parameters may be predictors of coronavirus disease 2019 (COVID-19) mortality. This study aimed to analyze the potential of D-dimer, ferritin, and lactate dehydrogenase (LDH) to predict mortality in severe COVID-19 patients.

Methodology: A retrospective cohort study, including 147 patients, was examined using secondary data from medical records of hospitalized COVID-19 patients. D-dimer, ferritin, and LDH levels were obtained from the patients' blood analysis on first hospitalization. Patients were then categorized into a survival group (97 patients) and a non-survival group (50 patients) based on final outcome. Proportions and means were analyzed using Chi square and Mann-Whitney tests. Further, the correlation and accuracy were analyzed using partial correlations test and receiver operating characteristic curve analysis. The combination of multiple predictors was also analyzed.

Results: The non-survival group had significantly higher levels of D-dimer (32.11 ± 13.05 vs. 9.57 ± 16.65; $p < 0.001$), ferritin (1719.84 ± 539.52 vs. 808.83 ± 664.81; $p < 0.001$), and LDH (1782.92 ± 1537.92 vs. 622.848 ± 274.79; $p < 0.001$) than the survival group. These parameters also had a moderate correlation with mortality ($r > 0.500$) and robust sensitivity and specificity for predicting mortality, especially ferritin (AUC = 0.906; sensitivity = 92.3%; specificity = 87.5%; $p < 0.001$), and the combination of ferritin and LDH with or without D-dimer (AUC = 0.959; sensitivity = 100%; specificity = 87.5%; $p < 0.001$).

Conclusions: The levels of these parameters are significantly higher, have robust sensitivity and specificity, and can be used as predictors of mortality.

Key words: COVID-19; D-dimer; ferritin; LDH; mortality.

J Infect Dev Ctries 2024; 18(9.1):S27-S32. doi:10.3855/jidc.18833

(Received 04 July 2023 – Accepted 09 February 2024)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been reported to have a high mortality rate in 215 affected countries, including Indonesia [1-4]. Laboratory findings can be used to determine the severity or mortality of COVID-19. Several laboratory parameters, including D-dimer, ferritin, and lactate dehydrogenase (LDH), can be used as biomarkers of inflammation, coagulation, and tissue damage for estimating COVID-19 severity [5].

Some studies have investigated the relationship between D-dimer, ferritin, LDH levels and COVID-19 [6-11]. Zhang *et al*. reported a correlation between D-dimer levels (with a cutoff point of ≥ 2.0 µg/mL) and the severity and mortality associated with COVID-19 [10]. Eloseily *et al.* stated that an increase in ferritin level above 700 ng/mL should be a cautionary marker for clinicians to conduct additional diagnostic tests for better therapeutic approaches; therefore, it is considered an important biomarker for COVID-19 management [11]. Giulia *et al*. concluded that LDH is a non-specific marker that tends to be higher in COVID-19 patients with severe symptoms [6]. Furthermore, COVID-19 infection elevates ferritin levels, followed by D-dimer and LDH levels [12,13]. The combination of several parameters (i.e., C-reactive protein (CRP), LDH, and ferritin ± D-dimer) can also predict the severity of COVID-19 [9].

The potential of D-dimer, ferritin, and LDH as significant predictors for COVID-19 severity or mortality has also been investigated in Indonesia; but not much is known about this association [14-16]. The current study attempts to investigate the possibility of using simultaneous or combination relationship of above parameters to predict COVID-19 mortality. Therefore, this study aims to analyze the potential of D-dimer, ferritin, and LDH to predict the mortality of COVID-19 patients, particularly those with severe conditions.

Methodology

Research design and participants

This study was conducted with a retrospective cohort design using secondary data from medical records of hospitalized COVID-19 patients from March 2020 to March 2021 at Dr. Wahidin Sudirohusodo Teaching Hospital, Makassar, South Sulawesi, Indonesia. This study enrolled 147 hospitalized patients who met the inclusion criteria, including positive COVID-19 test, severe symptoms, and complete laboratory records. Positive COVID-19 was detected using the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) quantitative reverse transcription polymerase chain reaction (RT-qPCR) molecular assay. Participants in the study were patients with severe symptoms diagnosed by internal medicine or pulmonary specialists according to the 10th edition of the International Classification of Diseases (ICD-10). Patients with mild or moderate diagnoses were excluded. Patients were also required to have complete laboratory records for D-dimer, ferritin and LDH. Comorbidities were not considered as exclusion criteria because a high percentage of severe patients had more than three comorbidities; and the sample size would be further minimized and not adequate by forcing exclusion with this variable. Patients were then categorized into a survival group (97 patients) and a non-survival group (50 patients) based on final outcome (alive or dead). The survival group included patients who improved their condition, whether they were still in the hospital or had recovered completely. Meanwhile, the non-survival group included patients who died ≤ 48 hours after hospitalization.

Procedures

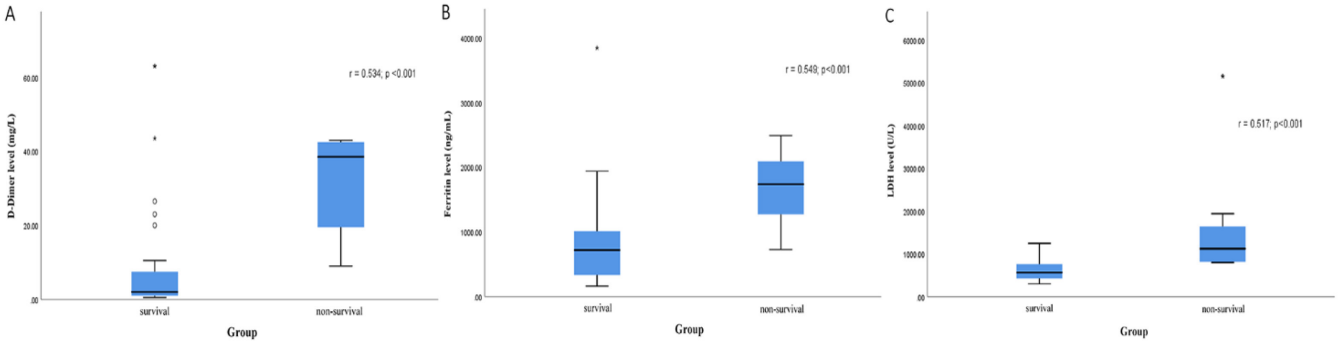
Medical records of COVID-19 inpatients were obtained from Dr. Wahidin Sudirohusodo Teaching Hospital after ethical approval from the Research Ethics Committee of the Faculty of Medicine, Hasanuddin University and Dr. Wahidin Sudirohusodo Teaching Hospital with reference number 428/UN4.6.4.5.31/PP36/2022. Data retrieved from medical records consisted of demographics (i.e., age and gender), comorbidities, and laboratory records. Comorbidities included clinical conditions with ICD-10 codes that were categorized as having 1–3, 4–5, and ≥ 6 comorbid conditions. The laboratory records were D-dimer, ferritin, and LDH levels measured from the patient's blood. D-dimer levels were measured using the Sysmex Coagulation System-2500 (CS-2500, Siemens, UK) with an immunoturbidimetric method (reference value < 0.5 mg/L). Ferritin levels were measured using an immunology analyzer (BioMerieux Vitek Inc., Hazelwood, MO, USA) with an enzyme-linked

Table 1. Demographic characteristics and mortality predictors of COVID-19 patients based on outcome.

Variables	Outcome status		*p value*
	Survival (n = 97)	Non-survival (n = 50)	
Demographic			
Age (years)	57.47 ± 12.69	64.92 ± 15.75	0.058
Age (category; years)			
18-40	14 (14.7)	4 (7.7)	0.050
41-60	46 (47.1)	8 (15.4)	
> 60	37 (38.2)	38 (76.9)	
Gender			
Male	60 (61.8)	31 (61.5)	1.000
Female	37 (38.2)	19 (38.5)	
Comorbidities			
1–3	13 (13.5)	1 (2.9)	0.220
4–5	49 (50.6)	29 (57.1)	
≥ 6	35 (36.0)	20 (40.0)	
Mortality predictors			
D-dimer (mg/L)	9.57 ± 16.65	32.11 ± 13.05	< 0.001
Ferritin (ng/mL)	808.83 ± 664.81	1719.84 ± 539.52	< 0.001
LDH (U/L)	622.848 ± 274.79	1782.92 ± 1537.92	< 0.001

Data are presented as n (%) and mean ± SD. Chi square test was used for categoric data and Mann-Whitney test for continuous data. COVID-19: coronavirus disease 2019; LDH: lactate dehydrogenase.

Figure 1. Correlation of mortality predictors with outcome in COVID-19 patients.



Mean levels of D-dimer (A), ferritin (B), and LDH (C) were higher in non-survival patients than in survival patients with a correlation coefficient > 0.5 and p value < 0.001. Circle (○) and asterisk (*) symbols indicate outlier data. COVID-19, coronavirus disease 2019; LDH, lactate dehydrogenase.

fluorescence assay (ELFA) method (reference value range: 18.7-323.0 ng/mL for men; 6.9-282.5 ng/mL for women). LDH levels were measured using the ABX Pentra 400 analyzer (Horiba Ltd, Kyoto, Japan) with a colorimetric enzyme-linked immunosorbent assay (ELISA) method (reference value range: 210-425 U/L). The reference values were those used by the hospital laboratory. The biomedical measurement procedure was performed when the patients were first admitted to the hospital for inpatient care.

Data analysis

Proportions and means were analyzed using bivariate analysis, including Chi square (χ^2) and Mann-Whitney tests. In addition, partial correlation test controlling for age, gender, and comorbidities; and receiver operating characteristic (ROC) curve test were performed to examine the correlation and accuracy of each predictor and their combination. The accuracy tested were sensitivity, specificity, and cut-off point. The combination of predictors included D-dimer + ferritin, D-dimer + LDH, ferritin + LDH, and D-dimer + ferritin + LDH. All analyses were performed using IBM SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY, U.S.A.) with a significance level of $\alpha = 0.05$ and a confidence level of 95%.

Results

A total of 147 COVID-19 patients, consisting of 97 survivors and 50 non-survivors were included in the study. There was no significant difference in mean age ($p > 0.05$), gender ($p = 1.000$), and comorbidities ($p = 0.222$). However, there were significant differences observed in D-dimer, ferritin, and LDH levels. The non-survival group had significantly higher levels of D-dimer (32.11 ± 13.05 vs 9.57 ± 16.65; $p < 0.001$), ferritin (1719.84 ± 539.52 vs 808.83 ± 664.81; $p < 0.001$), and LDH (1782.92 ± 1537.92 vs 622.848 ± 274.79; $p < 0.001$) compared to the survival group (Table 1).

Figure 1 shows that the D-dimer level was higher in the non-survival group compared to the survival group and had a significant correlation with mortality (r = 0.534, $p < 0.001$). ferritin and LDH levels also showed higher values in the non-survival group compared to the survival group and had a significant correlation with mortality (r = 0.549 and r = 0.517, $p < 0.001$, respectively).

The area under curve (AUC) values for D-dimer, ferritin, and LDH were 0.868 (95% CI: 0.760-0.976), 0.906 (0.807-1.000), and 0.894 (95% CI: 0.803-0.985), respectively. The sensitivity and specificity of D-dimer were 84.6% and 81.2%, respectively, with a cut-off point of 15.0. Ferritin had a cut-off point of 1168.25

Table 2. Analysis of receiver operating characteristic (ROC) curves for D-dimer, Ferritin, LDH, and their combinations in COVID-19 patients.

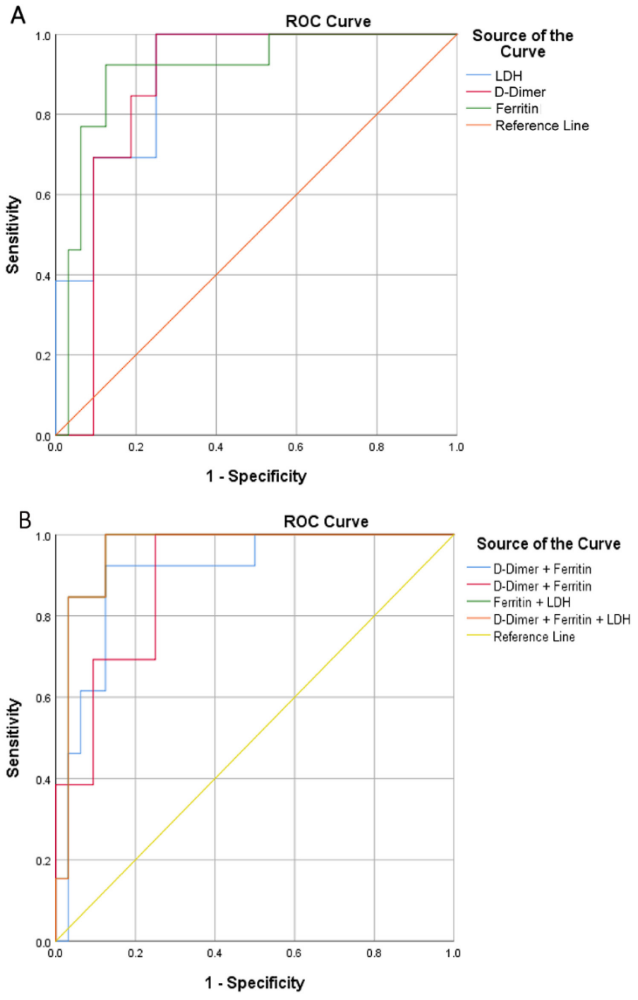
Predictors	Area under curve (AUC)	Sensitivity (%)	Specificity (%)	95% Confidence interval (CI)		*p-value*	Cut-off point
				Upper limit	Lower limit		
D-dimer	0.868	84.6	81.2	0.760	0.976	< 0.001	15.0
Ferritin	0.906	92.3	87.5	0.807	1.000	< 0.001	1168.25
LDH	0.894	100	75.0	0.803	0.985	< 0.001	782.5
D-dimer + Ferritin	0.899	92.3	87.5	0.800	0.998	< 0.001	
D-dimer + LDH	0.894	84.6	75	0.803	0.985	< 0.001	
Ferritin + LDH	0.959	100	87.5	0.902	1.000	< 0.001	
D-dimer + Ferritin + LDH	0.959	100	87.5	0.902	1.000	< 0.001	

COVID-19: coronavirus disease 2019; LDH: lactate dehydrogenase.

with a sensitivity of 92.3% and specificity of 87.5%. Finally, LDH had a sensitivity of 100% and specificity of 75% at a cut-off point of 782.5. The *p* values for all predictors were highly significant ($p < 0.001$; Figure 2 and Table 2).

The combination of D-dimer + ferritin had AUC of 0.899 (95% CI: 0.800–0.998) with sensitivity of 92.3% and specificity of 87.5% ($p < 0.001$). The combination of D-dimer + LDH had AUC of 0.894 (95% CI: 0.803-0.985) with a sensitivity of 84.6% and specificity of 75% ($p < 0.001$). The combination of ferritin + LDH had AUC of 0.959 (95% CI: 0.902-1.000) with a sensitivity of 100% and specificity of 87.5% ($p < 0.001$). Finally, the combination of D-dimer + ferritin + LDH had AUC of 0.959 (95% CI: 0.902–1.000) with a sensitivity of 100% and specificity of 87.5% ($p < 0.001$; Figure 2 and Table 2).

Figure 2. Receiver operating characteristic (ROC) curve of mortality predictors in COVID-19 patients.



A, ROC curve for each mortality predictor; B, ROC curve for different combinations of mortality predictors. COVID-19, coronavirus disease 2019; LDH, lactate dehydrogenase.

Discussion

This study aimed to analyze the relationship between three laboratory parameters (D-dimer, ferritin, and LDH) as potential biomarkers of mortality in severe COVID-19 infections in hospitalized patients. The study found that these three parameters were extremely elevated (above reference values) in both groups. This was expected due to the potential high percentage of comorbidities in COVID-19 patients (> 80% with more than three comorbidities) that may have led to the extreme high levels of these parameters. The current research did not treat comorbidities as an exclusion, because of the presence of comorbidities in a high percentage of patients. Therefore, these extremely elevated values should be considered with caution. However, the mean levels were significantly higher in non-survival group than in survival group with a ratio of approximately 3:1 for D-dimer, 2:1 for ferritin, and 2:1 for LDH. In line with this finding, a previous study reported that these parameters were significantly higher in the deceased group than in the intensive care unit (ICU) group while other parameters (e.g., C-reactive protein) were not significantly different [17]. Another study found that a high mortality rate in COVID-19 patients was associated with concomitant elevations in several parameters, including D-dimer, ferritin, and LDH [18]. This confirms that there is an association between laboratory findings and COVID-19 mortality. Despite the simultaneous significant increase in levels, the extreme values may still be expected to coexist with comorbid effects [19–21]. Therefore, it should be interpreted with caution.

COVID-19 is associated with several complications that can lead to significant physiological and biochemical changes [17]. In cases with severe symptoms, high D-dimer levels may indicate an abnormality in the blood coagulation process leading to common complications such as pulmonary micro-thrombosis and disseminated intravascular coagulation which can lead to death [22]. In addition, the elevated ferritin levels may be an effect of prolonged COVID-19 infection contributing to multiorgan dysfunction [22]. The severity of the infection also leads to the release of pro-inflammatory cytokines that can cause intracellular ferritin leakage, resulting in elevated ferritin levels and severe cellular damage [23]. Furthermore, COVID-19-induced tissue damage triggers the release of LDH into the circulation, particularly in severe interstitial pneumonia [22]. LDH also contributes to lactate production which leads to an increase in immunosuppressive cells and inhibition of cytolytic cells, thereby affecting the severity of the infection and

potentially resulting in death [24]. Therefore, the high levels of D-dimer, ferritin, LDH, and their consequences associated with severe cases of COVID-19 infection could be an indicator of mortality.

This study also showed that the three parameters included in this study have high sensitivity and specificity both individually and in combination. They can be used as reference biomarkers to predict the severity and even mortality of COVID-19 infection as reported in previous studies [17,18,25-27]. LDH showed the highest sensitivity of 100% with a cut-off value of 782.5. On the other hand, ferritin had the highest specificity of 87.5% with a cut-off value of 1168.25. D-dimer had a slightly lower but fairly similar sensitivity and specificity (84.6 and 81.2, respectively) with a cut-off value of 15.0 (Table 2). A previous study also reported a similarly large cut-off for these parameters, with ferritin two times higher than in the current study [28]. Although some findings contradict the cut-off result [10,13,29,30], these parameters were still reported higher in dead COVID-19 patients.

The combination of ferritin and LDH provided more accurate sensitivity and specificity compared to the other two-parameter combinations and showed no difference with the three-parameters combination (D-dimer + ferritin + LDH). This means that from a practical and cost-effective point of view, the combination of ferritin and LDH may serve as a sufficient alternative test instead of using all the parameters. Furthermore, these findings may also suggest that three parameters are better at predicting mortality than the severity in case of severe COVID-19 infection. Moreover, two-parameters combination (ferritin + LDH) may provide robust results even without adding other parameters such as CRP [9].

This study has several limitations. The sample size was small because the data associated with many patients was incomplete. In addition, most patients had mild and moderate symptoms, which was not taken into account in the current study. The methodological issue about selection bias may also be a concern. The comorbidities factor could not be considered as an exclusion criteria, because > 80% of the severe participants had more than three comorbidities. Forcing exclusion with this variable could lead to inadequate sample size. Therefore, the extreme value and cut-off point of the predictors should be considered with caution. The other factors not considered in this study should also be taken into account when considering the results, such as assay harmonization problems (in the case of D-dimer) [28], and the influence of the COVID-19 virus variants [31]. In addition, there may be other biomarkers that also contribute to the prediction of COVID-19 mortality.

However, future research on these biomarkers in predicting mortality of COVID-19, especially in the Indonesian population, need to address these limitations. The findings are still expected to be reliable and demonstrate the association between the elevated biomarker levels and COVID-19 mortality; however, the correction of the extreme value of the findings should be taken into consideration. Further investigation should compare participants with and without comorbidity to determine whether the extreme levels of biomarkers are a consequence of COVID-19 infection.

Conclusions

The levels of D-dimer, ferritin, and LDH were significantly higher in the non-survival group compared to the survival group in the case of hospitalized COVID-19 patients with severe symptoms. The biomarker analysis showed that those three parameters can be used as predictors of mortality. Ferritin had high sensitivity and specificity. The combination of ferritin and LDH with or without D-dimer also had robust sensitivity and specificity as a predictor of mortality.

Acknowledgements

We would like to thank the RIDONE agency (ridone.id.2022@gmail.com) for helping us with validating data and reviewing the manuscript.

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Conflict of interests: No conflict of interests is declared.