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Original Article

D-dimer Levels as Novel Biomarker Predictor for All-cause In-hospital Mortality Risk in COVID-19 Patients

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ABSTRACT

Background : Coronavirus disease 2019 (COVID-19) has affected people all around the world in varying degrees of severity, causing death. The global case fatality rate (CFR) due to COVID-19 was 2.2 % as of January 1st, 2021. The CFR in the Kediri district is 7.7%, which is higher than the Nasional CFR of 3%. In COVID-19, we looked at high D-dimer as one of the predictors of in-hospital mortality.
Objectives : The goal of this study was to find a link between D-dimer levels and all-cause in-hospital mortality in COVID-19 patients, as well as to define the best cut-off point.
Methods : A single-center cross-sectional study was conducted. From March to December 2020, 185 COVID-19 patients treated at Kediri General Hospital who were confirmed positive by RT-PCR matched the eligibility criteria. The levels of D-dimer were divided into two groups: those above and those below the cutoff point. We analyzed 4 cut of points, D-dimer ≥ 0.5 μg/ml, D-dimer ≥ 2 μg/ml, D-dimer ≥ 3 μg/ml, and D-dimer ≥ 4 μg/ml. The primary endpoint was all-cause in-hospital mortality. Data were collected retrospectively and processed using SPSS version 25.0.
Results : During hospitalization, 45 patients (24.3%) were died. Elevated D-dimer ≥ 4 μg/ml was statistically significant associated with all-cause inhospital mortality (adjusted odds ratio [OR] 3.46; 95% confidence interval [CI] = 1.41 – 8.49, p = 0.007), with a sensitivity of 82.1% and a specificity of 42.2% (area under curve [AUC] = 0.628; 95% CI = 0.527 – 0.728; p = 0.012).
Conclusion : Elevated D-dimer levels were associated with all-cause in-hospital mortality. In our study, the optimal cut of point D-dimer value was 4 μg/ml.

1. Introduction

Coronavirus disease 2019 (COVID-19) has spread among humans worldwide and infected over 80 million people as of January 1st, 2021.[1] WHO data on January 1st, 2021 shows as many as 1.8 million confirmed deaths, case fatality rate 2.2%. There are 221 affected countries and 180 local transmission countries, one of which is Indonesia. Data compiled by the Ministry of Health of the Republic of Indonesia until January 1st, 2021, states as many as 743. A total of 198 confirmed cases, with a case fatality rate of 3%, is higher than the global mortality rate.[2] Local transmission has occurred in Kediri, East Java, Indonesia. The case fatality rate in the Kediri district is 7,7% (189 out of 2448 confirmed cases), higher than the CFR in East Java which is around 6.93% (5900 deaths out of 85039 confirmed cases).[3,4] Based on these data, it is necessary to evaluate what causes the high mortality rate in Kediri district, especially in Kediri District Hospital (RSUD Kabupaten Kediri), as one of the leading referral hospitals for COVID-19 in the Kediri district area.

COVID-19 infection without symptoms, mild COVID-19 infection, moderate COVID-19 infection, severe COVID-19 infection, and critically ill COVID-19 infection COVID-19 infection can be found at a variety of phases.[5] Patients with severe COVID-19 are at risk for coagulopathy, including DIC and hypercoagulable condition, in addition to respiratory failure.[6,7] According to a recent meta-analysis by Boonyawat et al., the incidence of venous thromboembolism (VTE) among COVID-19 patients in ICU settings was 28%, while it was 10% in non-ICU settings.[8] D-dimers are protein fragments formed by fibrin clot breakdown that can be exploited as biomarkers for suspected VTE. We aimed to figure out the link between high D-dimer levels and in-hospital mortality in COVID-19 patients, as well as the optimum D-dimer cut-off value for predicting death.

2. Methods

2.1 Study Design

From the beginning of the pandemic in March through December 2020, a single-center retrospective investigation was undertaken in Kediri General Hospital in East Java. This study included all

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hospitalized patients over the age of 18 who had a positive COVID-19 real-time polymerase chain reaction.

2.2 Ethical approval

Our study was a retrospective medical record review of a COVID-19 patient database. This study has received approval from the local ethics of Kediri General Hospital.

2.3 Participants and eligibility criteria

Adult patients over 18 years old with laboratory results confirmed COVID-19 by RT-PCR method, mild to severe symptoms hospitalized at Kediri General Hospital, as one of the national referral hospitals for COVID-19, between March and December 2020 were included. Patients who had D-dimer results were included in the study. Exclusion criteria for this study were patients who were not examined for D-dimer levels, pregnant women, and patients whose outcome was unknown until the end of the study period. The clinical diagnosis of COVID-19 was made according to recent WHO guidelines. The endpoint was all-cause mortality during hospitalization. Figure 1 shows a flowchart of the study.

2.4 Measurement

Demographic data, history of present illness, past medical history, physical examination, blood oxygen saturation (SaO2) at admission, ECG, blood laboratory test collected within 24 hours after admission (hemoglobin, leucocyte, thrombocyte, D-Dimer), and Chest X-Ray. The D-dimer level was tested using an immunochromatography assay (Wondfo). The outcomes were collected from medical records and analyzed. Severe illness COVID-19 patients have Sp02 < 94 % on room air, Pa/FiO2 < 300 mmHg, respiratory rate more than 30 breaths per minute, or pulmonary infiltrates more than 50 %.(5) D-dimer levels were categorized into two groups, above and below the cut of point. We analyzed 4 cut of points, D-dimer ≥ 0.5 μg/ml, D-dimer ≥ 2 μg/ml, D-dimer ≥ 3 μg/ml, and D-dimer ≥ 4 μg/ml. The outcome was divided into two groups, survivor and in-hospital mortality.

2.5 Statistical analysis

Data were processed using SPSS software 25.0 for windows, IBM. Univariate analysis was performed for baseline characteristics. The normal distribution of quantitative variables was expressed as mean ± standard deviation (SD), while quantitative variables with abnormal distribution were represented as median (IQR). Categorical variables were presented as number and proportions (%). Categorical bivariate analysis was performed with the chi-square (χ2) or as an alternative Fisher's exact test. Numerical data were tested for normal and abnormal data distribution, then analyzed using an independent T-test and Mann Whitney, respectively. The variance was tested with Lavene's test. Kolmogorov-Smirnov tested data distribution. P <0.05 is used to denote significance for the primary outcome. All results will be presented in odds ratio (OR) format with a 95% confidence interval (CI). The backward approach of logistic regression was used to do multivariate analysis. Cut-off point, specificity, and sensitivity were determined using the receiver operating characteristic (ROC) curve and its area under the curve (AUC).

3. Results

3.1 Patients selection

Of the 262 patients who were confirmed RT-PCR COVID-19 from March to December 2020, 165 patients met the inclusion criteria. Patients hospitalized with severe to critical illness were 46.7 % (77/165).

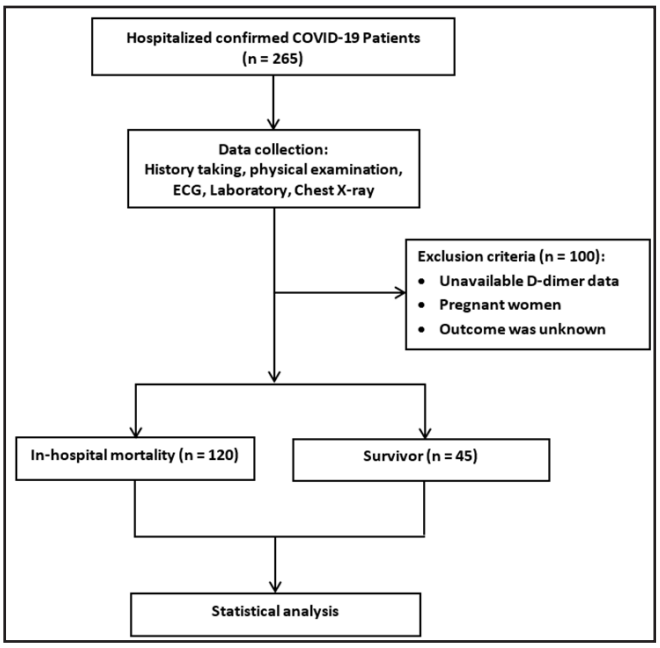

Figure 1. Study flowchart.
COVID-19 = coronavirus disease 2019; ECG = electrocardiogram.

3.2 Baseline characteristics

The median age was 54.1 years, ranging from 19 to 87 years. The number of elderly patients (≥ 60 years) was 28.5 % (47/165), and 48.5 % (80/165) were men. In general, the mean length of stay (LOS) was 9.7 ± 4.4 days. The most common symptom was cough and dyspnea, about 62.4% (103/165) and followed by fever 40 % (66/165). A history of illness often encountered is diabetes mellitus (26.1 %) and hypertension (22.4 %). Comparison of baseline characteristics, laboratory results, and X-rays on admission COVID-19 patients based on survival status is shown in table 1.

3.3 Main findings

The number of patients who died during hospitalization was About 27.3% of patients. Patients who died were statistically significantly older than those who survived (59 ± 17 vs. 54.5 ± 15 years; P <0.001). The proportion of elderly patients (over 60 years old) who died was higher (38.3% vs. 22.9%; P = 0.045). Systolic (130 ± 27 vs. 130 ± 31 mmHg; P = 0.854) and diastolic (70 ± 20 vs. 80 ± 20 mmHg; P = 0.259) blood pressure were not different between both groups. Heart rate patients who died was significantly higher (100 ± 29 vs. 93 ± 15; P-value = 0.002).

We analyzed several cut-of-point D-dimer values based on previous studies. A study conducted by Huang stated that D-dimer ≥ 0.5 μg/ml was significant in predicting inhospital mortality COVID-19 patients. (9) Several studies reported D-dimer level ≥ 2 μg/ml had higher mortality in COVID-19 patients.[10-12] Another research classified D-dimer values into groups (D-dimer <2x upper limit of normal (ULN), 2-3.9x ULN, 4-7.9x ULN, and >8x ULN.[13] In our study, patients with D-dimer value ≥ 0.5 μg/ml did not significantly differ in mortality (OR = 0.94; 95% CI = 0.42 – 2.10; p = 0.881). Patients who had D-dimer value ≥ 2 μg/ml had increased all-cause inhopital mortality (OR = 2.51; 95%CI = 1.23 – 5.13; p = 0.100). The proportion of deaths of patients with D-dimer ≥ 3 μg/ml was higher than patients who had D-dimer < 3 μg/ml (46.5 % vs. 20.5 %) with p value 0.010 (OR = 3.37; 95%CI = 1.61 – 7.09). About 48.7% of death happened to patients with D-dimer level ≥ 4 μg/ml, and statistically proven to predict all-cause inhospital mortality in COVID-19 patients (OR = 3.65; 95%CI = 1.71 –

Table 1. Baseline characteristics.

Variables	Output		P value
	In-hospital mortality (n = 45)	Survivor (n = 120)	
Age (year)	59 ± 17	54.5 ± 15	< 0.001
≥ 60 years old	18 (38.3 %)	29 (61.7 %)	0.045
< 60 years old	27 (22.9 %)	91 (77.1 %)	
Gender			
Male	19 (23.8 %)	61 (76.3 %)	0.324
Female	26 (30.6 %)	59 (69.4 %)	
Symptoms			
Febrile	19 (28.8 %)	47 (71.2 %)	0.721
Cough	27 (26.2 %)	76 (73.8 %)	0.694
Dyspnea	36 (35.0 %)	67 (65.0 %)	0.004
Sore throat	3 (15.8 %)	16 (84.2 %)	0.232
Stomache	7 (26.9 %)	19 (73.1 %)	0.965
Nausea & vomiting	18 (24.7 %)	55 (75.3 %)	0.502
Diarrhea	1 (10.0 %)	9 (90.0 %)	0.289
Malaise	22 (29.7 %)	52 (70.3 %)	0.523
Headache	2 (5.7 %)	33 (94.3 %)	0.001
Anorexia	0 (0 %)	11 (100%)	0.036
Decreased of consciousness	6 (33.3 %)	12 (66.7%)	0.578
History of illness			
Diabetes mellitus	15 (34.9 %)	28 (65.1 %)	0.192
Hypertension	6 (16.2 %)	31 (83.8 %)	0.086
Coronary artery disease	1 (33.3 %)	2 (66.7 %)	1.000
Heart failure	6 (66.7 %)	3 (33.3 %)	0.013
Asthma	0 (0 %)	1 (100 %)	1.000
COPD	0 (0 %)	1 (100 %)	1.000
Chronic kidney disease	1 (100 %)	0 (0 %)	0.273
Stroke	5 (71.4 %)	2 (28.6 %)	0.017
Systolic blood pressure (mmHg)	130 ± 27	130 ± 31	0.854
Diastolic blood pressure (mmHg)	78 ± 20	80 ± 20	0.259
Heart rate (bpm)	100 ± 29	93 ± 15	0.002
SpO2 < 94%	26 (38.2 %)	42 (61.8 %)	0.008
Febrile (T >38°C)	2 (16.7 %)	10 (83.3 %)	0.515

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Hypertension	6 (16.2 %)	31 (83.8 %)	0.086
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Heart failure	6 (66.7 %)	3 (33.3 %)	0.013
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SpO2 < 94%	26 (38.2 %)	42 (61.8 %)	0.008
Febrile (T >38°C)	2 (16.7 %)	10 (83.3 %)	0.515
Decreased of consciousness	5 (100 %)	0 (0 %)	0.001
Haemoglobin (g/dL)	13.4 ± 3	13.9 ± 2	0.631
Leukocytes (x10^3/ml)	10.3 ± 8.4	8.4 ± 4.4	0.088
Thrombocytes (x10^3/ml)	225.5 ± 147.3	268 ± 179.3	0.021
Severe illness	29 (37.7 %)	48 (62.3 %)	0.005
D-dimer ≥ 0.5 μg/ml	34 (27.0 %)	92 (73.0 %)	0.881
D-dimer ≥ 2 μg/ml	21 (40.4 %)	31 (59.6 %)	0.010
D-dimer ≥ 3 μg/ml	20 (46.5 %)	23 (53.5 %)	0.001
D-dimer ≥ 4 μg/ml	19 (48.7%)	20 (51.3%)	0.001
Chest X-Ray Pneumonia	41 (31.3 %)	90 (68.7 %)	0.027
Length of stay	7 ± 7	10 ± 5	<0.001

COPD = chronic obstructive pulmonary disease; SpO2 = peripheral oxygen saturation.

7.00; p = 0.001). Multivariate analysis using regression logistic with backward method shows D-dimer ≥ 4 μg/ml significantly increase inhospital mortality (OR = 3.46; 95%CI = 1.41 – 8.49; p = 0.007). Figure 2 decribes the discrimination of all-cause inhospital mortality using cut of point D-dimer ≥ 4 μg/ml (AUC = 0.622; 95% CI = 0.523 – 0.721; p = 0.014) with a specificity of 42.2% and a sensitivity of 82.1%.

4. Discussion

D-dimer is a fibrin degradation product that can be formed in several medical conditions. An increase in D-dimer level above 0.5 μg/ml can occur in infection, cancer, pregnancy, venous thromboembolism, and disseminated intravascular coagulation (DIC).[14] Coagulopathy has been reported in COVID-19 patients leading to hypercoagulabilities such as elevated D-dimer, fibrinogen, factor VIII, and sepsis-induced coagulopathy score (SIC score).[15]

An intersection between inflammation and coagulation factors is thought to be the mechanism behind hypercoagulability. A cytokine storm occurs when COVID-19 infection causes a rise in pro-inflammatory cytokines such as G-CSF, IP-10, IL-2, IL-6, IL-7, IL-10, MCP-1, MIP-1A, and TNF-α. This cytokine storm triggers an increase in inflammatory markers such as CRP, fibrinogen, LDH. Elevated IL-6 levels in the blood can induce tissue factor expression and initiate coagulation activation and thrombin formation. SARS-CoV-2 binds to ACE-2 receptors in the vascular endothelium, causing direct or indirect endothelial dysfunction, leading to thrombosis.[16]

International Society on Thrombosis and Haemostasis recommendations in enforcing VTE diagnosis for hospitalized COVID-19 patients, especially those critically ill, are to do risk stratification and check on D-dimer level. Imaging examinations are not recommended for routine diagnosis to prevent COVID-19 transmission. Elevated D-dimer above 1.5 μg/ml has a specificity of 88.5 % and a

Table 2. Bivariate and multivariate analysis of categoric variables associated with higher mortality.

Variable	Bivariate analysis		Multivariate analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Elderly, age ≥ 60 years old	0.045	2.09 (1.01 – 4.33)	0.049	2.26 (1.004 – 5.09)
SpO2 < 94%	0.008	2.54 (1.26 – 5.12)	-	-
Decrease of consciousness	0.001	4.00 (3.06 – 5.23)	0.021	20.58 (1.58 – 267.91)
Severe illness	0.005	2.72 (1.34 – 5.54)	0.030	2.40 (1.09 – 5.26)
Chest X Ray Pneumonia	0.027	3.30 (1.09 – 10.01)	0.085	2.84 (0.87 – 9.27)
D-dimer ≥ 0.5 μg/ml	0.881	0.94 (0.42 – 2.10)	0.079	0.43 (0.17 – 1.10)
D-dimer ≥ 2 μg/ml	0.010	2.51 (1.23 – 5.13)	-	-
D-dimer ≥ 3 μg/ml	0.001	3.37 (1.61 – 7.09)	-	-
D-dimer ≥ 4 μg/ml	0.001	3.65 (1.71 – 7.83)	0.007	3.46 (1.41 – 8.49)

CI = confidence interval SpO2 = peripheral oxygen saturation; OR = Odds ratio.

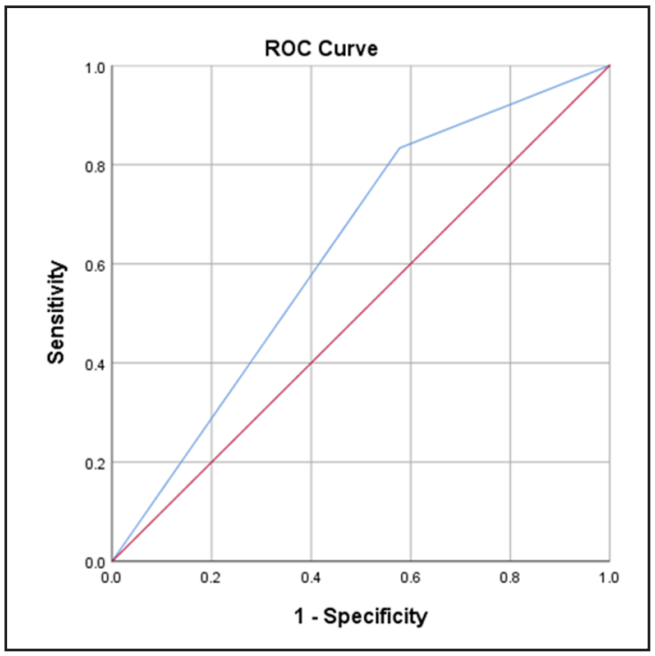

Figure 2. Receiver operating characteristics curve of D-dimer cut-off point.

sensitivity of 85%. Whereas D-dimer above 4 μg/ml has a poor outcome.[17]

The cut-off value for D-dimer levels that potentially predict all-cause in-hospital mortality is compared in our study. In our study, patients with D-dimer level ≥ 4 μg/ml statistically significant predicts all-cause in-hospital mortality in COVID-19 patients (OR = 3.65; 95%CI = 1.71 – 7.83; p = 0.001). These results are consistent with research conducted by Short et al.[13] Short et al. classified D-dimers into four groups: D-dimer <2x upper limit of normal (ULN), 2-3.9x ULN, 4-7.9x ULN, and >8x ULN, with the conclusion that a higher amount of D-dimer is linked to an increased risk of death.

Many studies have reported the optimal D-dimer cut-off point in predicting mortality COVID-19 patients is 2 μg/ml.[9-11] Meanwhile in our study, COVID-19 patients who had D-dimer value ≥ 2 μg/ml had increased all-cause inhopital mortality (OR = 2.51; 95%CI = 1.23 – 5.13; p = 0.10). But, multivariate analysis using regression logistic with backward method shows D-dimer ≥ 4 μg/ml significantly increase inhospital mortality (OR = 3.46; 95%CI = 1.41 – 8.49; p = 0.007). The AUC value of D-dimer ≥ 4 μg/ml shows discrimination (AUC = 0.628; 95% CI = 0.527 – 0.728; p = 0.012).

This study has several limitations. This study was a single-center cross-sectional study. The sample size was relatively small. Not all confirmed COVID-19 patients have D-Dimer levels checked. The D-dimer examination was only done on admission within 24 hours, so we did not know when the patients had worsening conditions. The D-dimer value in our laboratory machines has a lower limit of 0.1 μg/ml and an upper limit of 10 μg/ml. If a patient has a D-dimer value below 0.1 μg/ml or above 10 μg/ml, we can only categorize it into categorical data. Numerical data were not fully available, so the ROC curve could not be processed to assess the effective cut-off point D-dimer value.

5. Conclusion

Elevated D-dimer levels were associated with all-cause in-hospital mortality. In our study, the optimal cut of point D-dimer value was 4 μg/ml.

6. Declarations

6.1. Ethics Approval and Consent to participate
Not applicable.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

Not applicable.

6.6. Authors contributions
Idea/concept: NAN, MDHQ. Design: NAN, WSP, NKN. Control/supervision: NAN, MDHQ. Data collection/processing: NAN, WSP, NKN, PEN, SUP, MDHQ. Extraction/Analysis/interpretation: NAN, WSP, NKN, PEN, SUP, MDHQ. Literature review: NAN, WSP, NKN, PEN, SUP, MDHQ. Writing the article: NAN, WSP, NKN, PEN, SUP, MDHQ. Critical review: MDHQ, NAN. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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