Original Article

The Relation between D-Dimer, Hs-CRP, and ACE Inhibitor to Severity, Reinfection, and Mortality of COVID-19 Patients

Novita Silvana Thomas, Jatu Aphridasari, Ana Rima Setijadi

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, dr. Moewardi General Hospital, Surakarta, Indonesia

Abstract

Background: COVID-19 reinfection has been found, although the data is not clear yet. Pandemic conditions bring about limited facilities and infrastructure, so biomarkers are an option. Research on biomarkers and the use of ACE inhibitor drugs in COVID-19 patients has not been widely conducted in Indonesia.

Methods: This was a retrospective cohort study that used medical record data of confirmed COVID-19 patients treated at dr. Moewardi General Hospital for the period of January to March 2022. Surviving patients were observed for reinfections until November 2022.

Results: This study involved 524 medical records of confirmed COVID-19 patients. After exclusion and inclusion criteria, 517 medical records were obtained. D-Dimer cut-off values of ≥2435 were significantly related to severity (OR=2.05; 95% CI=1.38-3.06; P≤0.001) and mortality (OR=2.89; 95% CI=1.95-4.27; *P*≤0.001) of COVID-19 patients. Hs-CRP levels ≥4.59 were significantly associated with mortality in COVID-19 patients (OR=1.82; 95% CI=1.23-2.69; *P*=0.003). The use of ACE inhibitors (OR=0.55; 95% CI=0.33-0.89; *P*=0.015) was a protective factor from mortality but increased the risk of reinfection (OR=3.11; 95% CI=1.16-8.36; *P*=0.034).

Conclusion: D-Dimer and Hs-CRP biomarkers could be considered as predictor biomarkers for the severity and mortality of COVID-19 patients. Although the use of ACE inhibitors increased the risk of reinfection, it reduced the risk of mortality due to COVID-19.

Keywords: ACE, COVID-19, D-Dimer, Hs-CRP, inhibitor, reinfection

Corresponding Author:
Novita Silvana Thomas | Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Sebelas Maret, dr. Moewardi General Hospital, Surakarta, Indonesia | silvana.thomas@yahoo.com

Submitted: March 20th, 2023
Accepted: October 22nd, 2024
Published: October 31st, 2024

J Respirol Indones. 2024
Vol. 44 No. 4: 275–85
https://doi.org/10.36497/jri.v44i4.465

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This SARS-CoV-2 is causing deaths and an increase in confirmed cases despite global prevention efforts.[1] World Health Organization (WHO) global data showed more than 504.4 million confirmed cases on April 20, 2022, and about 6.2 million confirmed cases died.[2] Data in Indonesia, according to the COVID-19 Task Force, as of June 23, 2021, pointed out more than 6.3 million confirmed cases and 157,377 deaths.[3]

COVID-19 reinfections in individuals have been found and are still under study. Azam in 2020 obtained that the incidence of recurrent positive SARS-CoV-2 infection ranged from 7.3 to 21.4%.[4] Ozaras in 2020 observed patients experiencing a recurrent positive real-time reverse-transcription polymerase chain reaction (RT-PCR) with a previous history of symptom improvement and negative RT-PCR results.[5] Gao in 2021 stated that older age and women were at risk of recurrent positive COVID-19, while Adrielle et al in 2021 noted that reinfections were giving more severe symptoms than the previous episode.[6]

Risk factors for reinfections were health care workers and having blood type A. Comorbid hypertension, obesity, diabetes, and asthma were not associated with reinfection but affected the clinical severity of COVID-19 reinfections.[7] Qureshi et al 2022 mentioned a reinfection ratio of about 0.7% among 9,119 patients, while the average period of positive test results was 116±21 days. COVID-19 reinfection deaths were about 3.2%.[8] Many countries have confirmed reinfections raising questions about the effectiveness of vaccinations.[9]

The mortality ratio from COVID-19 was estimated at 3.4%, and comorbid conditions increase the risk of death.[10] A meta-analysis by Bolin et al. in 2020 named five diseases that increased the risk of COVID-19: hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and cerebrovascular disease.[11]

Petrovic in 2020 found that cardiovascular complications (22.2–31%) were the most common comorbid in COVID-19 patients of critical degrees.[12] Djaharuddin in 2020 obtained a mortality ratio of hospitalized COVID-19 patients of about 17.18%. Males aged ≥60 years had higher mortality. Hypertension, cardiovascular disease, and diabetes were comorbidities found in COVID-19 patients who did not survive.[13]

The COVID-19 pandemic brings about limited facilities and infrastructures, so biomarkers are an option to minimize exposure to health care if facilities are not available.[14] Biomarkers are related to progressivity and mortality due to COVID-19.[15] Huang et al in 2020 stated that an increase in D-dimer concentrations was associated with an increased risk of hypercoagulability and was a predictor of mortality in hospitals.[16]

Ponti in 2020 denoted C-reactive protein (CRP) as an inflammatory marker associated with the severity of COVID-19.[14] Biomarkers can be an efficient tool for prognostic stratification of COVID-19 patients, however, there is still limited information about which biomarkers can provide better prognostic value.[15] This study aimed to analyze the relation of D-dimer, Hs (high sensitivity) CRP, and the use of angiotensin-converting enzyme (ACE) inhibitor drugs to the severity, reinfection, and mortality of COVID-19 patients.

METHODS

This was an analytical observational study with a retrospective cohort approach. This study was conducted from November 2022 to January 2023. The consecutive sampling technique was used for this study.

The samples in this study were confirmed COVID-19 patients undergoing treatment at dr. Moewardi General Hospital Surakarta from January to March 2022 using secondary data from medical records with a total of 524 patients' medical records. Samples were divided into two groups. The first was the non-severe COVID-19 patients (moderate severity) described as having clinical pneumonia (fever, cough, shortness of breath, rapid breathing) without signs of severe pneumonia (e.g., oxygen saturation ≥93% in room air). The second group consisted of severe COVID-19 patients (severe or critical severity), defined as patients with clinical pneumonia plus one of these symptoms: a respiratory rate >30 times per minute, severe respiratory distress, or oxygen saturation <93% in room air, or patients with ARDS, sepsis, and septic shock.

The inclusion criteria were patients over ≥18 years old who were diagnosed with moderate, severe, or critical COVID-19 from RT-PCR or rapid diagnostic antigen (RDT-Ag) examination. Surviving patients were observed for reinfections until November 2022. The exclusion criteria were incomplete medical record data, patients or families could not be contacted, and patients diagnosed with COVID-19 reinfection longer than November 2022.

The data on D-dimer levels, Hs-CRP levels, and the use of ACE inhibitors, were collected at first admission when patients were treated at dr. Moewardi General Hospital Surakarta. Variables were analyzed for the relationship to the severity, reinfection, and mortality of COVID-19 patients. The author submitted research approval to the Ethics Eligibility Committee of dr. Moewardi Regional General Hospital Surakarta before the research was conducted.

The research data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 22, and the results were significant when the $P<0.05$. The research data were carried out analytical distribution tests using the Kolmogorov-Smirnov test because the number of samples was more than 50. The optimal cut-off value, sensitivity,

and specificity of D-dimer and Hs-CRP levels were assessed through the ROC curve. In this study, categorical data samples were analyzed using the chi-square test, while numerical data used the Mann-Whitney test. We used a logistic regression test for multivariate analysis.

RESULTS

This study involved 517 medical records of confirmed COVID-19 patients. The majority of COVID-19 patients aged 18-59 years (75.24%), were male (53.19%) and were not healthcare workers (97.87%). Confirmed COVID-19 patients had cardiovascular disease (17.02%), diabetes mellitus (17.02%), and other comorbidities such as malignancy, hypertension, kidney disorders, stroke, autoimmune (SLE), Human Immunodeficiency Virus (HIV), hepatitis, trauma, and pregnant conditions (50.29%).

The use of ACE inhibitors in COVID-19 patients was observed in 110 patients (21.28%). COVID-19 patients treated from January to March 2022 consisted of 361 (69.83%) non-severe patients and 156 (31.17%) severe patients. About 88.59% of patients had been vaccinated. There were 332 COVID-19 patients who survived (64.22%) and 17 (5.1%) patients experienced reinfection. An overview of the characteristics of the subject of study can be seen in Table 1.

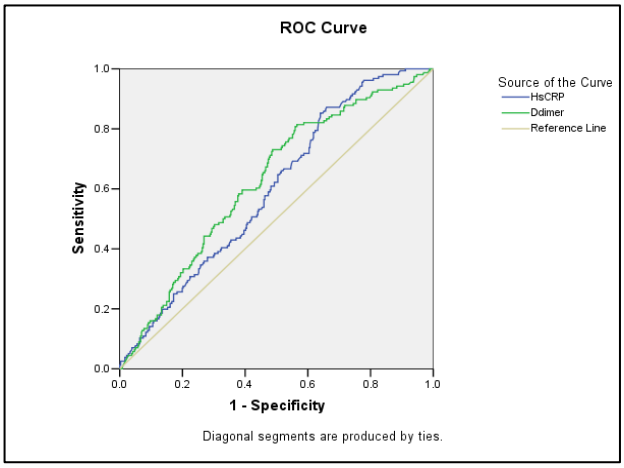

Figure 1. ROC curves of Hs-CRP and D-dimer based on the severity of COVID-19 patients.

The cut-off values of Hs-CRP and D-dimer were determined using the receiver operating characteristic (ROC) curve. The Hs-CRP level has an area under curve (AUC) value of 0.598. Hs-CRP has a sensitivity of 56.4% and a specificity of 54.0% to predict 59.8% of COVID-19 severity. Hs-CRP cut-off value of ≥4.59 mg/dl with *P*<0.001 indicated that Hs-CRP value ≥4.59 mg/dl was significant as a predictor of COVID-19 severity among patients. The ROC curve results were obtained based on the severity compared to the results of the Hs-CRP and D-Dimer examinations.

Table 1. Subject characteristics

Variable	N	%
Age		
≥60 years old	128	24.76
18-59 years old	389	75.24
Sex		
Male	275	53.19
Female	242	46.81
Occupation		
Non-health care worker	506	97.87
Health care worker	11	2.13
Cardiovascular disease		
Yes	88	17.02
No	429	82.98
Diabetes mellitus		
Yes	88	17.02
No	429	82.98
Other comorbid		
No	257	49.71
Yes	260	50.29
Malignancy	56	10.83
Hypertension	45	8.70
Kidney disease	43	8.38
Stroke	23	4.45
Autoimmune	10	1.93
HIV	9	1.74
Hepatitis	6	1.16
Others (<5 patients/cases)	64	12.38
Using ACE inhibitor		
Yes	110	21.28
No	407	78.72
Severity		
Non-severe	361	69.83
Severe	156	31.17
Vaccination status		
Not yet	59	11.41
Already	458	88.59
Mortality		
Death	185	35.78
Survive	332	64.22
Reinfection		
Yes	17	5.10
No	315	94.80

Table 2. Difference in Hs-CRP and D-Dimer levels by degree of severity of COVID-19 patients

Variable	Severe (n=156)	Non-severe (n=361)	*P*
Hs-CRP	9.19±10.01	6.99±8.20	<0.001**
D-Dimer	4506.50±4774.91	4366.69±14625.60	<0.001**

Table 3. Correlation of Hs-CRP, D-Dimer, and ACE inhibitor used to the severity of COVID-19 patients

Variable	Severity		Bivariate		Multivariate	
	Severe (n=156)	Non-Severe (n=361)	OR (95% CI)	*P*	OR (95% CI)	*P*
Hs-CRP						
≥4.59	88	166	1.52	0.029*	1.21	0.341
<4.59	68	195	(1.04-2.22)		(0.81-1.81)	
D-Dimer						
≥2435	93	144	2.22	<0.001**	2.05	<0.001**
<2435	63	217	(1.52-3.26)		(1.38-3.06)	
Using ACE inhibitor						
Yes	35	75	1.10	0.672	---	n/s
No	121	286	(0.70-1.74)			

D-dimer levels based on the ROC curve had an AUC value of 0.626, which means that D-dimer was able to predict 62.6% of the severity of COVID-19 with a sensitivity of 59.6% and a specificity of 60.1%. A cut-off value of ≥2435.00 with *P*<0.001 indicated that D-dimer ≥2435 ng/ml had significant results for the severity of COVID-19 patients.

This study divided COVID-19 patients into two groups of analysis based on the degree of severity. Severe and critical COVID-19) were observed in156 patients while non-severe (moderate) COVID-19 was seen in 361 patients. Patients with severe degrees had mean Hs-CRP levels of 9.19±0.01 and mean D-dimer levels of 4506±4774.91. The correlation of Hs-CRP, D-dimer levels, and the use of ACE inhibitors to the severity of COVID-19 patients were analyzed using chi-square in bivariate analysis and logistic regression in multivariate analysis.

Bivariate analysis showed that Hs-CRP levels ≥4.59 mg/dl (OR=1.52; 95% CI=1.04-2.22; *P*=0.029) had a significant association with the severity of COVID-19 patients with a 1.52 times higher risk of developing severe COVID-19 rather than patients with Hs-CRP levels <4.59 mg/dl. However, multivariate analysis showed that Hs-CRP levels ≥4.59 mg/dl (OR=1.21; 95% CI=0.81-1.81; *P*=0.341) were not significant with the severity of COVID-19 patients (*P*>0.05).

Analysis of D-dimer levels ≥2435 ng/ml showed a significant result on bivariate analysis (OR=2.22; 95% CI=1.52-3.26; *P*<0.001) and multivariate analysis (OR=2.05; 95% CI=1.38-3.06; *P*<0.001) to the severity of COVID-19 patients. Confirmed COVID-19 patients with D-dimer levels ≥2435 ng/ml have a 2-fold risk of having severe COVID-19. The use of ACE inhibitors showed no significant association in the results of bivariate or multivariate analysis. The results analysis of the relation between Hs-CRP, D-dimer, and the use of ACE inhibitors to the severity of COVID-19 patients can be seen in Table 2.

Hs-CRP levels ≥4.59 mg/dl showed a significant association on bivariate analysis (OR=2.13; 95% CI=1.47-3.07; *P*<0.001) and multivariate analysis (OR=1.82; 95% CI=1.23-2.69; *P*=0.003) to mortality of COVID-19 patients with *P*<0.01. Confirmed COVID-19 patients with Hs-CRP levels ≥4.59 mg/dl had a 1.82 times higher risk of mortality rather than Hs-CRP levels<4.59 mg/dl.

Analysis of D-dimer levels ≥2435 ng/ml in either bivariate (OR=3.04; 95% CI=2.09-4.42; *P*<0.001) or multivariate (OR=2.89; 95% CI=1.95-4.27; *P*<0.001) showed a significant association to mortality in COVID-19 patients with *P*<0.05. Confirmed COVID-19 patients with D-dimer levels ≥2435 ng/ml had a 2.89-3.04 times higher risk of mortality. The analysis showed that Hs-CRP and D-dimer can be considered as biomarkers and predictors of mortality in COVID-19 patients.

Table 4. Correlation of Hs-CRP, D-dimer, and ACE inhibitor use to mortality of COVID-19

Variable	Mortality		Bivariate		Multivariate	
	Yes (n=185)	No (n=332)	OR (95% CI)	*P*	OR (95% CI)	*P*
Hs-CRP						
≥4.59	113	141	2.13	<0.001**	1.82	0.003**
<4.59	72	191	(1.47-3.07)		(1.23-2.69)	
D-dimer						
≥2435	117	120	3.04	<0.001**	2.89	<0.001**
<2435	68	212	(2.09-4.42)		(1.95-4.27)	
Using ACE inhibitor						
Yes	33	77	0.72	0.154	0.55	0.015*
No	152	255	(0.46-1.13)		(0.33-0.89)	

Table 5. Hs-CRP relationship, D-dimer, and ACE inhibitor used to reinfection of COVID-19 patients

Variable	Reinfection		Bivariate		Multivariate	
	Yes (n=17)	No (n=315)	OR (95% CI)	*P*	OR (95% CI)	*P*
Hs-CRP						
≥4.59	8	133	1.22	0.694	---	n/s
<4.59	9	182	(0.46-3.24)			
D-Dimer						
≥2435	5	115	0 .72	0.553	---	n/s
<2435	12	200	(0.25-2.11)			
Using ACE inhibitor						
Yes	8	70	3.11	0.034*	2.42	0.197
No	9	245	(1.16-8.36)		(0.63-9.31)	

The use of ACE inhibitors in bivariate analysis showed insignificant results (OR=0.55; 95% CI=0.46-1.13; *P*=0.154) due to *P*>0.05. The results of multivariate analysis pointed out significant results (OR=0.55; 95% CI=0.33-0.89; *P*=0.015) so the use of ACE inhibitors was a protective factor from mortality. Confirmed COVID-19 patients who used ACE inhibitors had a 0.55 lower risk for mortality. The analysis results of the relation between Hs-CRP, D-dimer, and the use of ACE inhibitors to mortality of COVID-19 patients can be observed in Table 3.

The study found that of the 332 confirmed COVID-19 patients who survived, 17 patients (5%) had reinfection. Bivariate analysis of Hs-CRP levels ≥4.59 mg/dl (OR=1.22; 95% CI=0.46-3.24; *P*=0.694) revealed no association with the incidence of reinfection of COVID-19 patients. D-dimer analysis ≥2435 ng/ml to COVID-19 reinfection on bivariate analysis (OR=0.72; 95% CI=0.25-2.11; *P*=0.553) pointed out no association with the incidence of COVID-19 reinfection.

The use of ACE inhibitors (OR=3.11; 95% CI=1.16-8.36; *P*=0.034) in bivariate analysis obtained significant results in COVID-19 reinfection. Patients taking ACE inhibitors had a 3.1 times higher risk of developing reinfection than patients who did not use ACE inhibitors. However, multivariate analysis of Hs-CRP, D-dimer, and ACE inhibitor displayed no significant result for COVID-19 reinfection (*P*>0.05). The results of the analysis are shown in Table 4.

DISCUSSION

The majority of COVID-19-confirmed patients in this study were men (53.19%) and were following the research of Djaharuddin et al in 2020 in Indonesia.[13] A study from Zhou in 2020 showed higher ACE2 expression in men of Asian race.[17] Bwire in 2020 explained that men had higher ACE2 expression, immunological differences supported by women's production of hormones and the X chromosome as a protective effect, as well as men's lifestyles such as smoking.[18] High ACE2 receptors facilitate the entry of the SARS-CoV-2 virus which causes men to be more vulnerable against COVID-19 infection compared to women.[19] Sex hormones including estrogen and testosterone have a direct effect on the immune system that makes men more susceptible to COVID-19 infection.[20]

The majority of COVID-19 patients are under 60 years old (75.24%) and are non-healthcare workers (97.87%) because this productive age group often gathers for social and recreational activities, and takes preventive measures such as washing hands frequently, wearing masks, and appeals to stay at home.[18,21] Al-Kuwari et al in 2021 noticed that non-healthcare workers were more susceptible to COVID-19 due to a lack of awareness of precautions such as avoiding crowds, wearing masks, or washing hands.[21]

Confirmed COVID-19 patients in these patients mostly have comorbidities, especially cardiovascular disease, DM, and other comorbidities. Fathi et al in 2021 stated that comorbidities were considered a risk factor for infection in COVID-19 patients.[22] Comorbid involvement causes patients to be at higher risk of dying from COVID-19 infection.[13,22,23]

Djaharuddin in 2020 noted that hypertension, cardiovascular disease, and diabetes were comorbidities that were often found in COVID-19 patients.[13] Cardiomyocytes and the increased ACE2 in circulation were found in patients with hypertension, cardiovascular disease, and diabetes, causing patients with such comorbidities to be more susceptible to COVID-19 infection.[24,25]

Comorbid diabetes is a risk factor for the severity of the disease and poor outcomes in COVID-19 patients.[26] Our study observed about 88.59% of patients had been vaccinated. Islam in 2022 claimed that vaccinated patients had a much greater chance of developing moderate infections than unvaccinated patients.[9]

Vaccination will increase immunity, as patients who have received at least 1 dose of the vaccine have higher plasma anti-receptor binding domain (RBD) antibodies and a nearly 50-fold increase in neutralizing activity.[27] We found that there were 17 patients (5.1%) had experienced reinfections among confirmed COVID-19 patients who survived. Stamatatos et al in 2021 suggested that vaccination could lower the risk of reinfection.[28]

This study noticed that the cut-off value of Hs-CRP ≥4.59 mg/dl was significant to the severity of COVID-19. This study had a lower cut-off value because serum CRP is an acute-phase protein synthesized by the liver due to IL-6 stimulation. Hs-CRP levels were influenced by gender, ethnicity, acute degree of the disease, and time of taking.[29] The samples in this study were mostly non-severe COVID-19 patients, and the time of blood sampling for serum examination was not observed as an influencing factor. Bivariate analysis between severity and Hs-CRP levels ≥4.59 mg/dl showed a significant association. The more severe the severity of COVID-19, the higher the Hs-CRP value will be.[15,30]

Multivariate analysis showed that Hs-CRP levels ≥4.59 mg/dl were not significant to the severity of COVID-19. This happens because Hs-CRP is a biomarker influenced by age, gender, smoking, weight, fat levels, blood pressure, and liver damage.[16] Patients with myocardial infarction, stress, trauma, infection, inflammation, surgery, or malignancy can cause elevated Hs-CRP levels to be less specific.[29] D-dimer levels based on the ROC curve have a cut-off value of ≥2435 ng/ml. The research of He et al. in 2021 had a not much different cut-off, namely 2025 mg/mL.[31]

D-dimer levels ≥2435 ng/ml had a significant relation to severe COVID-19 in both bivariate and multivariate analyses.[32,33] The increase in D-dimer levels in COVID-19 patients was mainly due to the release of pro-inflammatory cytokines that caused inflammatory storms. Levels of pro-inflammatory cytokines such as IL-2, IL-7, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α in plasma are higher, especially in severe COVID-19 patients. T cells, macrophages, and natural killer cells cause this release, supported by studies of more than 150 inflammatory cytokines and chemical mediators resulting in microvascular system damage, abnormal activation of the coagulation system, pathological manifestations of systemic vasculitis, and extensive microthrombosis.[24,34]

Hypoxia that occurs in severe COVID-19 patients triggers molecular and cellular pathways that cause thrombosis.[35] Sepsis that occurs in severe COVID-19 patients affects blood clotting, such as elevated levels of PAI-1, and fibrinolysis, thus activating the coagulation cascade as well as causing thrombosis.[32]

The use of ACE inhibitors showed no significant association with severity in either bivariate or multivariate analyses. A meta-analysis from Singh in 2022 supported this study that using ACE inhibitors was neither associated with increased mortality nor the severity of disease progression in COVID-19 patients.[36] ACE2 was identified as the SARS-CoV-2 receptor, and its levels in circulation increased in patients taking ACE inhibitor drugs, which will be harmful to COVID-19 infection.[25,37]

However, some studies found that upregulating ACE2, especially in plasma, by ACE inhibitors, could prevent the virus from binding to lung cells, which could protect against SARS-CoV-2 infection in the lungs.[25,37,38] Increased ACE2 also leads to the degradation of angiotensin II and increased formation of angiotensin, which is beneficial for its vasodilating, anti-inflammatory, and antifibrotic effects, especially in patients with ARDS.[25,37]

Bivariate and multivariate analysis showed that Hs-CRP values ≥4.59 mg/dl had a significant association with mortality of COVID-19 patients. This research is supported by many studies that show Hs-CRP is a good predictive biomarker and correlates with a high risk of death in COVID-19 patients.[39,40] The study of Shabrawy et al in 2021 proposed cutting off of Hs-CRP serum of more than 33.9 ng/L with a sensitivity of 76.5% and a specificity of 88.9% to predict mortality in COVID-19.[40] Ahirwar et al in 2022 stated that Hs-CRP greater than 65.5 mg/L had a sensitivity of 93.8% and a specificity of 85.3% for predicting death in COVID-19.[41]

The cut-off value of D-dimer in this study was ≥2435 mg/dl, and the results of the analysis showed significant values for mortality in COVID-19 patients. Zhang in 2020 stated that D-dimer values of more than 2 µg/mL were predictors of mortality in COVID-19 patients.[42] In 2021 explained that the D-dimer value of 2025 mg/L was the optimal cut-off value as a predictor of mortality for COVID-19 patients.[32]

This study showed that D-dimer ≥2435 ng/ml in COVID-19 patients had a 2.89-3.04 times higher risk of mortality. Severe COVID-19 patients release more than 150 inflammatory cytokines and chemical mediators, causing microvascular damage, abnormal activation of the coagulation system, pathological manifestations of systemic vasculitis, and extensive microthrombosis.[24,34]

Sepsis and severe hypoxia in COVID-19 patients increase PAI-1 levels, and fibrinolysis causes thrombosis that increases D-dimer levels.[32,34,35] Gungor et al 2021 observed that D-dimer levels at the beginning of hospitalization were associated with severity and could predict mortality.[33]

The use of ACE inhibitors is a protective factor of mortality. Angiotensin II production decreases due to ACE inhibitors increasing the production of Ang-(1–7) by ACE2 and activation of Mas receptors, which act as anti-inflammatory and anti-fibrosis. The protective role of ACE inhibitors reduces lung injury thereby reducing severity and mortality.[43–45] Vasodilation, anti-inflammatory, antiproliferative, and antifibrotic effects by ACE2 receptors offset the effects of systemic damage from COVID-19.[37,46] The fourth edition of COVID-19 management guidelines and the European Society of Cardiology suggest continuing the use of ACE inhibitors or ARBs in patients who are already using them, as it may decrease mortality rates and the need for mechanical ventilation in COVID-19 patients.[19,47]

Our study showed patients taking ACE inhibitors had a 3.1 times higher risk of developing reinfection. ACE2 levels in circulation increased in patients taking ACE inhibitor drugs.[25] The attachment and fusion of the virus into the host cell begin when the virus' S protein binds to the host cell's receptor-binding domain (RBD), ACE2.[1,48] The affinity of the SARS-CoV-2 bond to ACE2 is 10-20 times stronger than that of SARS-CoV.[48]

So that ACE inhibitor users facilitate the entry of SARS-CoV-2 which facilitates infection or reinfection of COVID-19.[25,44] Hs-CRP and D-Dimer biomarkers cannot be used as predictors of reinfection of COVID-19 patients.[4] Hs-CRP levels of ≥4.59 mg/dl and D-Dimer ≥2435 ng/ml were not significant to the incidence of COVID-19 reinfection.

LIMITATION

The limitations of this research are the inadequate facilities and infrastructure to determine reinfection. There is a possibility of bias regarding the duration of ACE inhibitor use and its effect on mortality.

CONCLUSION

COVID-19 patients with D-dimer levels ≥2435 ng/ml had a 2-fold higher chance of experiencing severe COVID-19 and 3.04 times higher mortality compared to patients with D-dimer levels <2345 ng/ml. Patients with Hs-CRP levels ≥4.59 mg/dl had a 1.52 times higher chance of experiencing severe COVID-19 and 1.82 times higher mortality than Hs-CRP levels <4.59 mg/dl. D-Dimer and Hs-CRP can be considered as predictor biomarkers of the severity and mortality of COVID-19 patients. COVID-19 patients who take ACE inhibitors increase the risk of reinfection but reduce the risk of mortality due to COVID-19.

REFERENCES

1. Burhan E, Isbaniah F, Susanto AD, Yoga T, Aditama, Soedarsono, et al. Manifestasi klinis. In: Pneumonia COVID-19 diagnosis dan penatalaksanaan di Indonesia. 1st ed. 2015.
2. World Health Organization. World health statistics 2022: Monitoring health for the SDGs, sustainable development goals. 2022.
3. Satuan Tugas Penanganan COVID-19. Analisis Data COVID-19 Indonesia (Update Per 21 Agustus 2022) [Internet]. Satuan Tugas Penanganan COVID-19. 2022 [cited 2022 Aug 21]. Available from: https://covid19.go.id/p/berita/analisis-data-covid-19-indonesia-update-28-februari-2021
4. Azam M, Sulistiana R, Ratnawati M, Fibriana AI, Bahrudin U, Widyaningrum D, et al. Recurrent SARS-CoV-2 RNA positivity after COVID-19: A systematic review and meta-analysis. Sci Rep. 2020;10(1):20692.
5. Ozaras R, Ozdogru I, Yilmaz AA. Coronavirus disease 2019 re-infection: First report from Turkey. New Microbes New Infect. 2020;38:100774.
6. Gao L, Jiang D, Wen XS, Cheng XC, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res. 2020;21(1):83.
7. Adrielle dos Santos L, Filho PG de G, Silva AMF, Santos JVG, Santos DS, Aquino MM, et al. Recurrent COVID-19 including evidence of reinfection and enhanced severity in thirty Brazilian healthcare workers. Journal of Infection. 2021;82(3):399–406.
8. Qureshi AI, Baskett WI, Huang W, Lobanova I, Hasan Naqvi S, Shyu CR. Reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients undergoing serial laboratory testing. Clinical Infectious Diseases. 2022;74(2):294–300.
9. Islam MdZ, Riaz BK, Akbar Ashrafi SA, Farjana S, Efa SS, Khan MA. Severity of COVID-19 reinfection and associated risk factors: Findings of A cross-sectional study in Bangladesh. medRxiv. 2022;1.
10. Amirfakhryan H, safari F. Outbreak of SARS-CoV2: Pathogenesis of infection and cardiovascular involvement. Hellenic Journal of Cardiology. 2021;62(1):13–23.
11. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with covid-19: Evidence from meta-analysis. Aging. 2020;12(7):6049–57.
12. Petrovic V, Radenkovic D, Radenkovic G, Djordjevic V, Banach M. Pathophysiology of cardiovascular complications in COVID-19. Front Physiol. 2020;11:575600.

13. Djaharuddin I, Munawwarah S, Nurulita A, Ilyas M, Tabri NA, Lihawa N. Comorbidities and mortality in COVID-19 patients. Gac Sanit. 2021;35 Suppl 2:S530–2.
14. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57(6):389–99.
15. Peiró ÓM, Carrasquer A, Sánchez-Gimenez R, Lal-Trehan N, del-Moral-Ronda V, Bonet G, et al. Biomarkers and short-term prognosis in COVID-19. Biomarkers. 2021;26(2):119–26.
16. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther Adv Respir Dis. 2020;14:1753466620937175.
17. Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3.
18. Bwire GM. Coronavirus: Why men are more vulnerable to Covid-19 than women? SN Compr Clin Med. 2020;2(7):874–6.
19. Perhimpunan Dokter Paru Indonesia (PDPI), Perhimpunan Dokter Spesialis Kardiovaskular Indonesia, Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia, Perhimpunan Dokter Anestesiologi dan Terapi Intensif Indonesia, Ikatan Dokter Anak Indonesia. Pedoman tatalaksana COVID-19. 4th ed. Burhan E, Susanto AD, Isbaniah F, Nasution SA, Ginanjar E, Pitoyo CW, et al., editors. Pedoman tatalaksana COVID-19 edisi 4. Indonesia; 2022.
20. Lau ES, McNeill JN, Paniagua SM, Liu EE, Wang JK, Bassett I V., et al. Sex differences in inflammatory markers in patients hospitalized with COVID-19 infection: Insights from the MGH COVID-19 patient registry. PLoS One. 2021;16(4):e0250774.
21. Al-Kuwari MG, AbdulMalik MA, Al-Nuaimi AA, Abdulmajeed J, Al-Romaihi HE, Semaan S, et al. Epidemiology characteristics of COVID-19 infection amongst primary health care workers in Qatar: March-October 2020. Front Public Health. 2021;9:679254.
22. Fathi M, Vakili K, Sayehmiri F, Mohamadkhani A, Hajiesmaeili M, Rezaei-Tavirani M, et al. The prognostic value of comorbidity for the severity of COVID-19: A systematic review and meta-analysis study. PLoS One. 2021;16(2):e0246190.
23. Shahid Z, Kalayanamitra R, McClafferty B, Kepko D, Ramgobin D, Patel R, et al. COVID-19 and older adults: What we know. J Am Geriatr Soc. 2020;68(5):926–9.
24. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116(10):1666–87.
25. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: Celebrating the 20th anniversary of the discovery of ACE2. Circ Res. 2020;126(10):1456–74.
26. Norouzi M, Norouzi S, Ruggiero A, Khan MS, Myers S, Kavanagh K, et al. Type-2 diabetes as a risk factor for severe covid-19 infection. Microorganisms. 2021;9(6):1211.
27. Abbasi J. Study suggests lasting immunity after COVID-19, with a big boost from vaccination. JAMA - Journal of the American Medical Association. 2021;326(5):376–7.
28. Stamatatos L, Czartoski J, Wan YH, Homad LJ, Rubin V, Glantz H, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science (1979). 2021;372(6549):1413–8.
29. Burtis CA, Bruns DE. Cardiovascular disease. In: Tietz - Fundamentos de Química Clínica e Diagnóstico Molecular. 7th ed. Missouri: Elsevier Inc.; 2015. p. 1560–99.
30. Liu Z, Wu D, Han X, Jiang W, Qiu L, Tang R, et al. HsCRP variation is the main risk factor for clinical outcome in COVID-19 hospitalized

young and middle-aged patients. Res Sq. 2020;7:1–19.
31. Farshidfar F, Koleini N, Ardehali H. Cardiovascular complications of COVID-19. JCI Insight. 2021;6(13):e148980.
32. He X, Yao F, Chen J, Wang Y, Fang X, Lin X, et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Sci Rep. 2021;11(1):1830.
33. Gungor B, Atici A, Baycan OF, Alici G, Ozturk F, Tugrul S, et al. Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: A systematic review and meta-analysis. American Journal of Emergency Medicine. 2021;39:173–9.
34. Perhimpunan Dokter Spesialis Kardiovaskular Indonesia. Diagnosis kasus cardiovascular pada pasien COVID-19. In: Firdaus I, Sukmawan R, Santoso A, Juzar DA, editors. Panduan diagnosis dan tatalaksana penyakit kardiovaskular pada pandemi COVID-19. 1st ed. Jakarta: H&B PERKI; 2020.
35. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res. 2019;181:77–83.
36. Singh R, Rathore SS, Khan H, Bhurwal A, Sheraton M, Ghosh P, et al. Mortality and severity in COVID-19 patients on ACEIs and ARBs—A systematic review, meta-analysis, and meta-regression analysis. Front Med (Lausanne). 2022;8:703661.
37. Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ace-inhibitors and arbs in covid-19 patients. Elife. 2020;9:e57278.
38. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102–8.
39. Sabah Khalid S, Mohamed Ali Z, Faris Raheem M. Serum levels of homocysteine, troponin-I, and high sensitive c-reactive protein in Iraqi COVID-19 patients. Journal of Contemporary Medical Sciences. 2022;8(3):189–93.
40. El-Shabrawy M, Alsadik ME, El-Shafei M, Abdelmoaty AA, Alazzouni AS, Esawy MM, et al. Interleukin-6 and C-reactive protein/albumin ratio as predictors of COVID-19 severity and mortality. The Egyptian Journal of Bronchology. 2021;15(1):5.
41. Ahirwar AK, Takhelmayum R, Sakarde A, Rathod BD, Jha PK, Kumawat R, et al. The study of serum hsCRP, ferritin, IL-6 and plasma D-dimer in COVID-19: A retrospective study. Horm Mol Biol Clin Investig. 2022;43(3):337–44.
42. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324–9.
43. Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 (Covid-19) and cardiovascular disease: A viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. J Am Heart Assoc. 2020;9(7):e016219.
44. South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin–angiotensin system inhibition during the COVID-19 pandemic. Nat Rev Nephrol. 2020;16(6):305–7.
45. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020;81(5):537–40.
46. Khan KS, Reed-Embleton H, Lewis J, Bain P, Mahmud S. Angiotensin converting enzyme inhibitors do not increase the risk of poor outcomes in COVID-19 disease. A multi-centre observational study. Scott Med J. 2020;65(4):149–53.
47. Baigent C, Windecker S, Andreini D, Arbelo E, Barbato E, Bartorelli AL, et al. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: Part 1-epidemiology, pathophysiology, and diagnosis. Eur Heart J. 2022;43(11):1385–412.
48. Machhi J, Herskovitz J, Senan AM, Dutta D, Nath B, Oleynikov MD, et al. The natural history, pathobiology, and clinical manifestations of

SARS-CoV-2 infections. Journal of Neuroimmune Pharmacology. 2020;15(3):359–86.