Predisposing Factors of Cardiovascular Events among COVID-19 Patients

by Santoso Jaeri

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Research

Predisposing Factors of Cardiovascular Events among COVID-19 Patients

Devina Gabriella Nugroho[1], Putri Rachmawati Dewi [2], Rima Adjani Nugroho[1], Santoso Jaeri [3,4]

[1] K.R.M.T Wongsonegoro Hospital Semarang Indonesia
[2] Dept of Cardiovascular Medicine, K.R.M.T Wongsonegoro Hospital Semarang Indonesia
[3] Dept of Medical Biology and Biochemistry, Faculty of Medicine, Universitas Diponegoro, Semarang Indonesia
[4] Dept of Neurology National Hospital Diponegoro, Universitas Diponegoro, Semarang Indonesia

Corresponding author - santoso@fk.undip.ac.id

Abstract

Background COVID-19 is an infectious respiratory disease caused by SARS-CoV-2. During hospitalization, there is the possibility of cardiovascular events. The presence of these events might be related to some factors, unfortunately, there is limited evidence for these issues.

Objective The aim of the study was to determine the independent predisposing factors associated with the occurrence of the cardiovascular event among COVID-19 patients during hospitalization.

Method A retrospective study using medical records of hospitalized COVID-19 patients in K.R.M.T Wongsonegoro Hospital Semarang Indonesia, periods of June to September 2020. One hundred and one patients were included in the study. The subjects were classified into CVE groups and non-CVE, then the demographic characteristics and clinical data were collected. The Chi-Square, the Independent-T as well Mann-Whitney U test were used. The logistic regression then was used to determine the odds ratio of predisposing factors for CVE occurrence.

Results There were significant associations for the history of cardiovascular disease, smoking, hypertension, use of angiotensin-converting enzyme inhibitor agents, the level of blood glucose and troponin I, and the systolic blood pressure at the first visit for CVE occurrence. Furthermore, the history of CVD increased the risk 0,007 times to get CVE.test.

Conclusion The history of cardiovascular disease, smoking, hypertension, use of angiotensin-converting enzyme inhibitor agents, the level of blood glucose and troponin I, and the systolic blood pressure at first visit are the predisposing factors for the development of CVE among COVID-19 patients and patient who has the history of CVD have a high risk to get CVE during hospitalization.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was initially identified in Wuhan, Hubei, China in December 2019. It is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has spread rapidly globally. The respiratory symptoms are the main manifestation of COVID-19, but some patients may also present with cardiovascular events (CVE) such as coronary artery disease (CAD), congestive cardiac failure (CHF), arrhythmia, and stroke. A study of 5700 patients has reported hypertension (56.6%), CAD (11.1%), and CHF (6.9%) as common underlying comorbidities in confirmed COVID-19 cases.[1]

Studies from China demonstrated that 15–40% of COVID-19 patients have a history of cardiovascular disease (CVD) and 10–30% of patients show laboratory signs of cardiac injury and cardiovascular involvement. These findings are associated with a severe clinical course. Another study among 44,672 cases reported that there is a five-fold increase in case of fatality rates in patients with underlying CVD compared to patients without CVD (10.5% vs 2.3%).[1,2]

The COVID-19 infection is initiated through the binding of spike protein (S-protein) of SARS-CoV-2 with the host angiotensin-converting enzyme 2 (ACE-2) receptor. ACE-2 receptor is highly expressed in the pulmonary epithelial cells, cardiac myocytes, and vascular endothelial cells. The loss of ACE-2 receptor expression on the vascular endothelium may exacerbate endothelial dysfunction, inflammation, thrombosis, and induction of cytokine release through dysregulation of renin-angiotensin-aldosterone system (RAS).[1] These cellular effects are translated into exacerbation of underlying CVD or new onset of CVE.[1]

COVID-19 is associated with increased cardiac biomarkers levels due to myocardial injury and infection-induced myocarditis and ischemia. In a study by Shi et al. among died-COVID-19 patients, cardiac injury was commonly found (19.7%) including CAD (10.6%), CHF (4.1%), and stroke (5.3%).

Severe COVID-19 is also potentially associated with cardiac arrhythmias at least in part due to infection-related myocarditis.[4]

However, there is limited evidence especially in Indonesia regarding the predisposing factors that may contribute to the occurrence of CVE among COVID-19 patients during hospitalization. Herewith we provide evidence regarding this issue to provide get a better understanding of the risk factors for the occurrence of CVE among COVID-19 patients to improve the awareness and comprehensive management of COVID-19 patients to increase the survival rate of COVID-19 patients.

METHODS

The retrospective observational study among medical records of the hospitalized COVID-19 patients in K.R.M.T. Wongsonegoro Hospital Semarang Indonesia periods of June to September 2020 was conducted. All of the medical records of hospitalized COVID-19 patients which had complete records were obtained. The data including the demographical data, clinical data including clinical parameters, laboratory and radiological findings were collected as well as the occurrence of CVE.

The samples (N=101) were divided into two groups, first group was the patients with CVE during hospitalization (n=66). CVE was defined as the occurrence of an arrhythmia, CHF, CAD, and stroke during hospitalization. The second group was the patients without CVE during hospitalization (n=35).

The collected data then were entered to SPSS for Windows version 26, classified based on the occurrence of CVE. The numerical data such as age, blood pressure, heart rate, respiratory rate, body temperature, oxygen saturation, and the laboratory findings were tested for the normality of distribution using Kolmogorov–Smirnov test, then analyzed using an independent t-test for age and heart rate, and Mann-Whitney U test for other variables because the data distributions are not normal.

The categorical data such as sex, history of CVD such as acute myocardial infarction, stroke, or peripheral arterial occlusion, history of smoking, history of dyslipidemia, history of diabetes mellitus, history of hypertension, and history of ACE-inhibitor medication were classified based on the occurrence of CVE, then the comparison of these data between groups was determined using Chi-square and Fisher's exact test. The multivariate analysis using logistic regression was performed to determine what predisposing factors that significantly contribute to the occurrence of CVE among COVID-19 patients during hospitalization.

This study was approved by The Local Research Ethics Committee and the ethical clearance was obtained from K.R.M.T. Wongsonegoro Hospital Semarang Indonesia with the ethical certificate number 0347/KEPK /VI/2020.

RESULTS

Demographic dan Clinical Characteristics of Subjects

This study included 101 patients of COVID-19 in KRMT Wongsonegoro Hospital Semarang Indonesia, 66 of them developed CVE (65.3%) and 35 without CVE (34.7%). The demographic characteristics of the subject were depicted in Table 1, and the clinical findings from subjects at the first visit were demonstrated in Table 2.

Table 1 demonstrated that there was a significant difference in the history of cardiovascular disease, history of smoking, history of hypertension, and history of use of angiotensin-converting enzyme inhibitor (ACE-inhibitor), but no for other demographic characteristics among the CVE group compared to the non-CVE group.

Table 1. Demographic Characteristics of Subjects (N=101)

Variables	CVE (n=66) n (%) Mean ± SD	Non- CVE (n=35) n (%) Mean ± SD	p value
Sex			
Male	41 (68,3)	19 (31,7)	0,445
Female	25 (62,1)	16 (39)	
Age (years)	53,7 ± 0,03)	51,6 ± 11,14	0,339
History of cardiovascular disease			
Yes	45 (95,7)	2 (4,3)	0,000*)
No	21 (38,9)	33 (61,1)	
Dyslipidemia			
Yes	10 (62,5)	6 (37,5)	0.794
No	56 (65,9)	29 (34,1)	
History of smoking			
Yes	37 (77,1)	11 (22,9)	0,018*)
No	29 (54,7)	24 (45,3)	
History of chronic kidney disease			
Yes	11 (84,6)	2 (15,4)	0,210
No	55 (62,5	33 (37,5)	
History of diabetes mellitus			
Yes	29 (56,9)	22 (43,1)	0.070
No	37 (74)	13 (26)	
History of hypertension			
Yes	41(100)	0 (0)	0,000*)
No	25 (41,7)	35 (58,3)	
History of ACE-inhibitor medication			
Yes	8 (100)	0 (0)	0,048 *)
No	58 (62,7)	35 (37,6)	

SD: Standard Deviation, ACE: Angiotensin-Converting Enzyme, CVE: Cardiovascular event
*) : p , 0,05

Table 2 provides information that there was a significant difference in systolic blood pressure among the CVE group compared to non-CVE at the first visit to the hospital, but no difference for others.

Table 2. Clinical Findings of Subjects in the First Visit (N=101)

Variables	CVE (n=66) Median (IQR)	Non- CVE (n=35) Median (IQR)	p value
Systolic blood pressure (mmHg), median (IQR)	140 (90-237)	120 (91-139)	0,000*)
Heart rate, median (IQR)	95 (62-146)	100 (64-125)	0,339

Respiratory rate, median (IQR)	24 (18-50)	24 (20-38)	0,925
Body temperature (°C), median (IQR)	37,45 (35,8-39)	37 (36-39,6)	0,508
Oxygen saturation, median (IQR)	96 (40-99)	97 (56-100)	0,061

mmHg: millimeter mercury, IQR: Interquartile range, °C: degree Celsius
*) : p < 0,005

Laboratory Findings during Hospitalization

The laboratory findings among subjects during hospitalization were shown in Table 3. Table 3 demonstrated that there is no significant difference in most of the laboratory findings among both groups except for the blood glucose levels and troponin I levels.

Table 3. Laboratory and Radiological Findings among Subjects (N=101)

Variables	CVE (n=66) Median (IQR)	Non- CVE (n=35 Median (IQR)	p-value
Hemoglobin (mg/dL)	13.75 (7.9-17.2)	13.6 (7.4-22.6)	0.587
White blood cell (x10³/µl)	10.2 (4-37.8)	9.4 (5.1-27.2)	0.414
Platelet (x10³/µl)	245.5 (92-551)	251 (131-489)	0.719
Neutrophil lymphocyte ratio (/µl)	6.67 (1.05-38.89)	5.83 (1.07 14.29)	0.394
Blood glucose (mg/dL)	162 (92-434)	224 (91-139)	0.015*)
Ureum	29.5 (11-301.3)	32 (16.4-102)	0.713
Creatinine (µmol/l)	1.75 (0.3-22)	0.7 (0.2-3.5)	0.369
Natrium (mmol/l)	133 (114-143)	133)118-140)	0.446
Kalium (mmol/l)	4 (2.8-6.8)	3.9 (2.9-4.9)	0.906
Calcium (mmol/l)	1.17 (1.02-1.32)	1.2 (1.02-1.32)	0.161
Troponin I (ng/ml)	0.022 (0.001-8233)	0.0064 (0.0002 0.1988)	0.002*)

IQR: Interquartile range, mg/dL: milligrams/decilitter, l; microliters, mmol/l: millimole/litter, mol/l: micromole/litter
*): p < 0,005

Cardiovascular Disease Event

The analysis was continued to determine the predisposing factors of the cardiovascular event using the multivariate analysis. Before doing the analysis, we classified some of the variables with numerical scale into categorical scale including systolic blood pressure, blood glucose levels, and troponin I based on the criteria from World Health Organization.

The results of the multivariate analysis were depicted in Table 4. According to table 4, it is concluded that in the presence of other predisposing factors for CVE occurrence among COVID-19 patients, the history of prior CVD is the independent risk factor for CVE occurrence with an odds ratio of 0,007. It means that COVID-19 patients having a history of CVD before being diagnosed with COVID-19 have a 0,007 times higher risk of having CVE during hospitalization.

Table 4. Multivariate analysis for determination of predisposing factors for cardiovascular events among COVID-19 patients

Variables	p-value	Adjusted OR	95% CI
High systolic blood pressure	1,000	0,978	0,000 -
Hyperglycemia	0,146	5,795	0,541 – 62,019
History of smoking	0,877	0,853	0,114 – 6,396
History of CVD	0,000 *)	0,007	0,001 – 0,089
History of Hypertension	0,999	0,000	0,000 -
High troponin I level	0,365	4,526	0,173 – 118,451
History of ACE-inhibitor	0,998	0,000	0,000 -

DISCUSSION

Coronavirus disease 2019 (COVID-19) has the main manifestation the respiratory symptoms, but some patients may also present with cardiovascular events (CVE) like acute coronary syndrome (ACS) and congestive cardiac failure (CHF), arrhythmia, and stroke.[1] The occurrence of CVE among COVID-19 patients increases the case fatality rates of COVID-19.[1,2] However, there is limited evidence especially in Indonesia regarding the predisposing factors that may contribute to the occurrence of CVE among COVID-19 patients during hospitalization. Herewith we provide evidence that some predisposing factors contribute to the CVE event among COVID-19 patients during hospitalization such as the history of cardiovascular disease, smoking, hypertension, use of ACE-inhibitor agents, the level of blood glucose levels and troponin I, and the systolic blood pressure at the first visit. Furthermore, the patient who has a history of CVD before being diagnosed with COVID-19 has a 0,007 times higher risk of CVE during hospitalization.

A cohort study of 191 patients from Wuhan, China showed that hypertension in 30%, diabetes mellitus (DM) in 19%, and CVD in 8% as main comorbidity of COVID-19.[3,4] The cardiovascular risk factors including male sex, advanced age, diabetes, hypertension, and obesity as well as patients with the established cerebrovascular and cerebrovascular disease have been identified as particularly vulnerable populations with increased the risk of morbidity including the occurrence of CVE and mortality among COVID-19 patients. It is similar to our study that there is an association between the history of cardiovascular disease, smoking, hypertension, and the use of ACE-inhibitor agents for the development of CVE among COVID-19 patients during hospitalization.

Smoking is one of the most common cardiovascular risk factors. The mechanisms by which cigarette smoking induces and promotes atherosclerosis and atherothrombosis are complex and interconnected. The key pathways are inflammation, endothelial dysfunction, prothrombotic, altered lipid metabolism, insulin resistance, and demand-supply mismatch. Smoking is also known to be responsible for the

increased release of catecholamines, which exert cardiovascular effects such as increased heart rate, vasoconstriction, and increased cardiac output. COVID-19 patients with a history of tobacco use could make such patients susceptible to severe symptoms, thereby increasing the chance of death.[5, 6, 7] Meta-analysis study by Zhao et al. showed that there is a statistically significant association between smoking and the severity of COVID-19 outcomes (Odds Ratio (OR) 2.0 (95% CI 1.3 – 3.1).[8] Bivariate analysis of this study found that the history of smoking was significantly different among the group with CVE compared to non CVE.

The history of diabetes mellitus has been associated with major comorbidity in COVID-19 patients. The role of diabetes mellitus affects susceptibility to SARS-CoV-2 infection is still in debate. Some studies provide evidence that the prevalence of diabetes mellitus in people infected with the virus is about the same as in the general population.[9,10] Our study showed that the history of diabetes mellitus may be contributing to the exacerbation or occurrence of new CVE among COVID-19 patients.

The clinical presentation of COVID-19 patients at the first visit also might be contributing to the occurrence of CVE. Our data presented that high systolic blood pressure (SBP) was significantly associated with CVE occurrence among COVID-19 patients. It is approved that COVID-19-induced CVE occurred through the binding of SARS-CoV-2 with ACE-2 receptor which is expressed in the lungs, heart, and vessels. ACE-2 receptor is a key member of the renin-angiotensin system (RAS) which is important to maintain blood pressure. In the study of Caillon in 2021, among 157 COVID-19 patients, 120 were discharged and 37 died found that the majority (68.3%) of patients with hypertension and systolic blood pressure were identified as a covariate in both mortality and survival prediction models of COVID-19.[2,9]

Troponin I may be elevated in patients with COVID-19 with cardiac involvement and should be obtained in patients with such suspicion. StA study by Huang et al in 2020, the level of hypersensitive troponin I (hs-cTnI) was increased substantially in patients having g virus-related cardiac injury. Study among 138 hospitalized patients with COVID-19 in Wuhan, China, the elevated high-sensitivity cardiac troponin I (hs-cTnI) was present in 7.2% of patients overall and 22% of patients who required ICU care.[11, 12] Our study demonstrated that the troponin I level among CVE group is significantly increase compared to the o non-CVE group.

Hyperglycemia is associated with poor prognoses, while better glycemic control is closely associated with improvement in clinical outcomes in COVID-19 patients.[13] Study by Jean et al in 2020 stated that infection leads to profound alterations in whole-body metabolism. Sustained inflammation affects systemic glucose homeostasis and contributed to hyperglycemia. They also found that blood glucose was significantly higher in patients with severe COVID-19 than those with mild COVID-19 (WMD 2.21, 95% CI: 1.30–3.13, $P < 0.001$, $I^2 = 0\%$).[9,10] Unfortunately, we did not identify the mortality, and our study demonstrated that the blood glucose level in our study was significantly higher (p=0.015) in a non-CVE group compared to CVE patients.

The mechanisms of CVE among COVID-19 are complex. It may result from the effect of the cytokine release storm. The cytokine storm originated from the imbalance of T cell activation with dysregulated release of interleukin (IL)-6, IL-17, and other cytokines induce acute lung injury, which leads to increased cardiac workload, potentially problematic in patients with the presence of heart failure, unfortunately, we did not assess the measurement of the IL-6, IL-17, and other cytokines in order to gain the better understanding of this mechanism. In addition, we used secondary data from the medical records which have potency for the recall biases.[3]

CONCLUSION

The history of cardiovascular disease, smoking, hypertension, use of angiotensin ACE-inhibitor agents, the level of blood glucose and troponin I, and the systolic blood pressure at first visit are the independent predisposing factors for the development of CVE among COVID-19 patients during hospitalization. A patient who has a history of CVD before being diagnosed with COVID-19 has the risk of 0,007 times to have CVE during hospitalization.

Conflict of Interest and Funding Resource

The authors stated no conflict of interest.

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