Medical Comorbidities as Predictors of COVID-19 Short-Term Mortality: A Historical Cohort Study

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Abstract

Background: While the coronavirus disease 2019 (COVID-19) is most commonly associated with the respiratory system, disorders in other organ systems, such as the cardiovascular, neurologic, or renal, can also contribute to disease fatality. This study aimed to evaluate the relation of comorbidities to COVID-19 short-term mortality. Method: This was a single-center observational study with a historical cohort method at Bethesda Hospital Yogyakarta, Indonesia. COVID-19 diagnosis was made by utilizing reverse transcriptase-polymerase chain reaction (RT-PCR) on nasopharyngeal swabs. Patient data were retrieved from electronic medical records and used for Charlson Comorbidity Index assessments. In-hospital mortality was monitored throughout their hospital stay. Results: This study enrolled 333 patients. According to the total number of comorbidities in Charlson, 11.7% (n=39) of patients had no comorbidities; 30.9% (n=103) of patients had one comorbidity; 20.1% (n=67) of patients had two comorbidities; and 37.2% (n=124) of patients had more than three comorbidities. In multivariate analysis, these variables were significantly related to short-term mortality in COVID-19 patients: older age (odds ratio [OR] per year 1.64; 95% confidence interval [CI] 1.23-2.19; p 0.001), myocardial infarction (OR 3.57 ; 95% CI 1.49-8.56; p: 0.004), diabetes mellitus (OR 2.41; 95 CI 1.17-4.97; p: 0.017), renal disease (OR 5.18 ; 95% CI 2.07-12.97; p <0.001), and longer duration of stay (OR 1.20; 95% CI 1.08-1.32; p <0.001). Conclusion: Our study revealed multiple risk factors for mortality in patients with COVID-19. The coexistence of cardiovascular disease, diabetes, and renal problem are significant predictors of short-term mortality in COVID-19 patients.

INTRODUCTION

Coronavirus disease (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the first incidence of SARS-CoV-2 infection was discovered in December 2019 in Wuhan, Hubei Province, China, the disease has escalated at an alarming rate.[1,2] As of 1 November 2021, World Health Organization (WHO) had confirmed 246,357,468 cases of COVID-19 worldwide, including 4,995,412 casualties.[3] While the causative SARS-CoV-2 virus predominantly affects the respiratory system, problems in other organ systems, such as the cardiovascular, neurologic, and renal, can also contribute to disease fatality.[4,5]

In a previous study in China, 344 patients with COVID-19 were admitted to the intensive care unit. One hundred thirty-three people died on the 28th day, with a median survival of 25 days. Numerous patients have a variety of comorbidities.[6] Additionally, another study in China found that 247 of 633 COVID-19 patients had at least one comorbidity.[7]

In Indonesia, data on medical comorbidities and COVID-19 prognosis are limited. The objective of this study is to evaluate the relation of comorbidities to COVID-19 short-term mortality. Additionally, we would like to investigate the relationship between specific comorbidities and COVID-19 short-term mortality.

METHODS

Study Design and Clinical Data

This was a cohort study conducted at Bethesda Hospital Yogyakarta, Indonesia. We enrolled individuals who tested positive for COVID-19, made by utilizing reverse transcriptase-polymerase chain reaction (RT-PCR) on nasopharyngeal swabs. Patient data were retrieved from electronic medical records. The dataset contains demographic information, including age, gender, length of stay, and information about the comorbidities.

Outcome

The primary outcome that was evaluated was short-term mortality. In this study, the term short-term mortality refers to in-hospital mortality. Comorbidities' mortality burden was quantified in this study using the Charlson comorbidity index. The Charlson comorbidity index is a widely used tool for predicting mortality by identifying or weighing comorbidities. Health researchers widely use it to quantify disease burden and case mix.[8] The index's performance was evaluated using the tenth revision of the International Classification of Diseases (ICD-10). The following ICD-10 codes were used to define the various comorbidities in this study: diabetes (E10, E11), cardiovascular disease (I25), hypertension (I10-I15), asthma (J45), chronic obstructive pulmonary disease (J44), acute kidney injury (AKI; N17), chronic kidney disease (N18), and dementia diagnoses (F00-04, F05.1, G30, G31, A81.0).

Statistical Analysis

Data descriptive analysis was carried out using Microsoft Excel®, and statistical analysis was performed using SPSS software. We evaluated discrete variables to determine the risk factor for short-term mortality in COVID-19 patients with and without comorbidities. The t-test, Mann-Whitney test, and χ2test statistics were used to determine differences in study variables between groups. We used Cox proportional hazard models to determine whether comorbidities were predictive of in-hospital mortality. A proportional sub-distribution hazards model analysis was utilized, in which death is represented as a competing risk. The univariate models' significant predictors were then included in multivariate models, adjusting for possible confounding variables. The proportional hazard assumption was tested for all reported variables. Odds ratios with 95% confidence intervals were obtained. A two-sided p-value of 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Bethesda Hospital ethical committee and clinical research division. Likewise, this study followed the ethical principles outlined in the 1964 Helsinki Declaration and its following revisions.

RESULTS

This study enrolled 333 patients with a median age of 59 (19-91) years, with a proportion of patients aged less than 50 years being 23.4% (n=78); 50-50 years being 28.5% (n=95); 60-69 years being 27.3% (n=91); 70-79 years being 15.3% (n=51); and >80 years being 5.4% (n=18). In total, 58.6% of patients (n=195) were male and 41.4% were female (n=138).

According to the total number of comorbidities enrolled in Charlson, 11.7% (n=39) of patients had no comorbidities, 30.9% (n=103) of patients had one comorbidity, 20.1% (n=67) of patients had two comorbidities, and 37.2% (n=124) of patients had more than three comorbidities. Diabetes mellitus (33.6%, n=112) and cerebrovascular disease (25.2%, n=84) were the two most common comorbidities reported by patients in this study. Patients were hospitalized for an average of 8 (1-37) days throughout treatment. The median age of COVID-19 patients who died was 67 (26-91) years, whereas the median age of COVID-19 patients who survived was 57 (19-86) years.

The unadjusted analysis revealed that the following variables contribute to a greater likelihood of death in patients with COVID-19: older patient age, greater comorbidities, longer hospital stay, and several types of comorbidities in the patient. In multivariate analysis, these variables were significantly related to short-term mortality in COVID-19 patients: older age (odds ratio [OR] per year 1.64; 95% confidence interval [CI]

1.23-2.19; p 0.001), myocardial infarction (OR 3.57 ; 95% CI 1.49-8.56; p: 0.004), diabetes mellitus (OR 2.41; 95 CI 1.17-4.97; p: 0.017), renal disease (OR 5.18 ; 95% CI 2.07-12.97; p <0.001), and longer duration of stay (OR 1.20; 95% CI 1.08-1.32; p <0.001).

Table 1. Baseline chanracteristics of patients with COVID-19

Characteristics	All participants (n=333)	Deceased (n=83)	Alive (n=250)
Age, median, years	59 (19-91)	67 (26-91)	57% (19-86)
<50	23.4% (78)	10.8% (9)	27.6% (69)
50-59	28.5% (95)	19.3% (16)	31.6% (79)
60-69	27.3% (91)	33.7% (28)	25.2% (63)
70-79	15.3% (51)	22.9% (19)	12.8% (32)
>80	5.4% (18)	13.3% (11)	2.8% (7)
Sex, %(n)	Sex, %(n)	Sex, %(n)	Sex, %(n)
Male	58.6% (195)	66.3% (55)	56% (140)
Female	41.4% (138)	33.7% (28)	44% (110)
Weighted Charlson comorbidity index, %(n)	Weighted Charlson comorbidity index, %(n)	Weighted Charlson comorbidity index, %(n)	Weighted Charlson comorbidity index, %(n)
0	11.7% (39)	2.4% (2)	14.8% (37)
1	30.9% (103)	18.1% (15)	35.2% (88)
2	20.1% (67)	15.7% (13)	21.6% (54)
>3	37.2% (124)	63.9% (53)	28.4% (71)
Comorbidities within the Charlson comorbidity index, %(n)	Comorbidities within the Charlson comorbidity index, %(n)	Comorbidities within the Charlson comorbidity index, %(n)	Comorbidities within the Charlson comorbidity index, %(n)
Myocardial infarction	11.4% (38)	24.1% (20)	7.2% (18)
Congestive heart failure	15.3% (51)	24.1% (20)	12.4% (31)
Cerebrovascular disase	25.2% (84)	31.3% (26)	23.2% (58)
Chronic pulmonary disease	3.6% (12)	4.8% (4)	3.2% (8)
Ulcer disease	0.6% (2)	0% (0)	0.8% (2)
Mild liver disease	0.3% (1)	1.2% (1)	0% (0)
Diabetes mellitus	33.6% (112)	49.4% (41)	28.4% (71)
Hemiplegia	1.2% (4)	0% (0)	1.6% (4)
Renal disease	11.4% (38)	27.7% (23)	6% (15)
Diabetes wih end organ damage	0.6% (2)	0% (0)	0.8% (2)
Any malignancy	0.9% (3)	0% (0)	1.2% (3)
AIDS	0.9% (3)	2.4% (2)	0.4% (1)
Length of stay, median, day	8 (1-37)	7 (1-26)	8% (1-37)

Table 2. Unadjusted and multivariate analysis of factors associated with mortality in adults with COVID-19 (n =333).

	Unadjusted results	Unadjusted results	Multivariate results	Multivariate results
Characteristics	Death with COVID-19, OR (95% CI)	p-Value	Death with COVID-19, OR (95% CI)	p-Value
Age, median, years	**1.06 (1.04-1.08)**	**< 0.001**	**1.64 (1.23-2.19)**	**0.001**
Sex	Sex	Sex	Sex	Sex
Male	1.54 (0.92-2.59)	0.101	1.54 (0.81-2.93)	0.189
Female	Ref		Ref	
Weighted Charlson comorbidity index	Weighted Charlson comorbidity index	Weighted Charlson comorbidity index	Weighted Charlson comorbidity index	Weighted Charlson comorbidity index
0	Ref		Ref	
1	3.15 (0.69-14.48)	0.140	1.78 (0.36-8.76)	0.476
2	4.45 (0.95-20.91)	0.058	1.67 (0.31-8.98)	0.548
>3	**13.81 (3.19-59.86)**	**<0.001**	5.20 (0.93-29.18)	0.061
Comorbidities within the Charlson comorbidity index	Comorbidities within the Charlson comorbidity index	Comorbidities within the Charlson comorbidity index	Comorbidities within the Charlson comorbidity index	Comorbidities within the Charlson comorbidity index
Myocardial infarction	**4.09 (2.04-8.20)**	**<0.001**	**3.57 (1.49-8.56)**	**0.004**
Congestive heart failure	**2.24 (1.20-4.20)**	**0.012**	0.85 (0.35-2.11)	0.733
Cerebrovascular disase	1.51 (0.87-2.62)	0.141	1.05 (0.50-2.21)	0.898
Chronic pulmonary disease	1.532 (0.449-5.223)	0.496	1.26 (0.22-7.09)	0.796
Ulcer disease	4,986,033,534	0.999		
Mild liver disease	4,925,228,246	1.000		
Diabetes mellitus	**2.46 (1.48-4.10)**	**0.001**	**2.41 (1.17-4.97)**	**0.017**
Hemiplegia	0.000	0.999		
Renal disease	**6.01 (2.95-12.21)**	**<0.001**	**5.18 (2.07-12.97)**	**<0.001**
Diabetes wih end organ damage	0.000	0.999		
Any malignancy	0.000	0.999		
AIDS	6.15 (0.55-68.69)	0.140	13.41 (0.85-210.70)	0.065
Length of stay, median, day	**1.10 (1.03-1.18)**	**0.004**	**1.20 (1.08-1.32)**	**<0.001**

Abbreviations: AIDS, acquired immune deficiency syndrome; CI, confidence interval; OR, odds ratio.

DISCUSSION

Our findings showed that myocardial infarction (OR 3.57 ;95% CI 1.49-8.56; p: 0.004), diabetes mellitus (OR 2.41; 95% CI 1.17-4.97; p: 0.017), and renal disease (OR 5.18 ; 95% confidence CI 2.07-12.97; p <0.001) are significant prognostic factors for short-term mortality in COVID-19 patients. Multiple comorbidities are associated with the severity of COVID-19 disease progression. These findings support a prior systematic review that demonstrated that patients with COVID-19 disease who also have comorbidities such as hypertension or diabetes mellitus are more likely to acquire a more severe course and progression of the disease.

Older patients, particularly those 65 years and older who have comorbidities and are infected, have a higher likelihood of ICU admission and mortality from COVID-19.[9] Age-related immune cell defects associated with a more vigorous inflammatory response have been proposed as a possible explanation for the elderly's increased mortality.[10]

Numerous poor outcomes associated with COVID-19 have been linked to cardiovascular disease. This, however, may be a direct outcome of cardiovascular disease or may be a result of other comorbidities occurring concurrently with the cardiovascular disease.[11] The pathophysiology behind the connection between cardiovascular disease and COVID-19 is unclear, although they may involve infection-related demand ischemia that progresses to myocardial injury or dysfunction or a viral-induced inflammatory storm that results in shock and subsequent ischemic injury. Additionally, a recent case report discovered evidence of myocardial infection caused directly by the virus.[12]

Type 2 diabetes patients were also more likely to have a more severe COVID-19 infection. The results of a prior cohort study of 7337 patients with COVID-19 who had type 2 diabetes and those who did not demonstrate that individuals with type 2 diabetes required more interventions during their hospital stay compared to those who did not.[11]Patients with poor blood glucose control showed a significantly higher overall death rate than those with proper glucose control.[13] Numerous mechanisms have been proposed to link diabetes and COVID-19, including a weakened immune system, a pre-existing proinflammatory state, direct pancreatic injury, and dysregulation of angiotensin-converting enzyme 2 (ACE2) signaling.[14,15]

A previous study indicated that COVID-19 patients with renal disease had a higher mortality rate, with stage 2 and stage 3 AKI patients having a 3.5- and 4.7-fold greater mortality, respectively than those with normal kidney function.[16] COVID-19's specific pathophysiologic link with kidney disease is uncertain. However, ACE2 appears to have a role. ACE2 has been identified as the receptor for SARS-CoV-1 and was recently confirmed as a cell entry receptor for SARS-CoV-2.[17,18] ACE2s are expressed in a wide variety of organs, most notably the gastrointestinal tract and kidney. ACE2 expression is about 100 times more in the kidneys than in the lungs in human tissue RNA sequencing; consequently, kidneys with substantial ACE2 expression may be the primary target of SARS-CoV-2 infection.[19] Past studies examining the renal histopathologic findings in COVID-19 support the hypothesis of SARS-CoV infection occurring directly in the kidney.[20,21]

COPD was not found to be a significant predictive factor in our study. This is in contrast to earlier studies. Among other comorbidities, chronic obstructive pulmonary disease (COPD) has been linked to a poor prognosis. A meta-analysis of multiple studies conducted in China indicated that patients with pre-existing COPD identified with COVID-19 had a fourfold increase in death. The smoking status of patients and the severity of COVID-19 were not considered in this investigation. Only one previous study discovered a link between smoking and a severe course of COVID-19.[22]

When age and sex were adjusted for, a higher Charlson Comorbidity Index score was associated with an increased risk of severe COVID-19 and short-term mortality. This study adds to prior research indicating that individual comorbidities are independent risk factors for poor COVID-19 outcomes.[23,24] Our findings may help guide epidemic modeling, public health, and clinical decisions about the COVID-19 pandemic's management. As a result, individuals with comorbidities should take all necessary precautions to avoid contracting SARS CoV-2, as they typically have a poor prognosis.

Numerous limitations apply to this study. First, it was based on the results of a retrospective analysis of medical records, which may have been lacking in information about symptoms and prior conditions. Second, this study focused only on a short-term prognosis. Additional research is needed to establish the effect of comorbidities on COVID-19 outcomes and determine whether other validated comorbidity indexes can accurately predict poor COVID-19 outcomes.

CONCLUSION

Our study revealed multiple risk factors for mortality in patients with COVID-19. The coexistence of cardiovascular disease, diabetes, and renal problem are significant predictors of short-term mortality in

COVID-19 patients.

DATA AVAILABILITY

The data generated for this study are accessible upon request to the corresponding author.

CONFLICT OF INTEREST

The authors state that no conflict of interest existed during the conduct of this study.

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