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Original Article

More severe comorbidities, advanced age, and incomplete vaccination increase the risk of COVID-19 mortality

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Abstract

Numerous studies have stated that comorbidities are risk factors for coronavirus disease 2019 (COVID-19) mortality, but few have considered the severity or stage of these comorbidities. The aim of this study was to determine the association between the severity of comorbidity, age, and number of COVID-19 vaccinations with COVID-19 mortality. This case-control study was conducted from July 2021 until December 2022 at the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The patients were divided into non-survived patients (case group) and survived patients (control group). The inclusion criteria for cases were adult patients hospitalized with confirmed COVID-19, based on reverse transcriptase-polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs. Using total sampling, 1,046 confirmed COVID-19 patients, which consisted of 450 (43%) non-survived patients and 596 (57%) survived patients, were included. The most common comorbidity was diabetes mellitus (DM) (82.7%), chronic kidney disease (CKD) (43%), hypertension (25.7%), and obesity (23.6%). Our multivariate analysis indicated that older age (aOR: 1.03; 95%CI: 1.02–1.04, p<0.001), male sex (aOR: 1.29; 95%CI: 1.11–2.00, p=0.007), severe COVID-19 at first admission (aOR: 3.13; 95%CI: 2.08–4.73, p<0.001), having pneumonia (aOR: 1.99; 95%CI: 1.21–3.33, p=0.005), poorly controlled DM with HbA1c≥9% (aOR: 2.90; 95%CI: 1.72–4.89, p<0.001), severe obesity with body mass index (BMI)≥30 (OR: 2.90; 95%CI: 1.72–4.89, p<0.001), hypertension stage 2 (aOR: 1.99; 95%CI: 1.12–3.53, p=0.019) or stage 3 (aOR: 6.59; 95%CI: 2.39–18.17, p<0.001), CKD stage 3 (aOR: 2.50; 95%CI: 1.36–4.59, p=0.003), stage 4 (aOR: 5.47; 95%CI: 2.18–13.69, p<0.001) or stage 5 (aOR: 1.71; 95%CI: 1.04–2.81, p=0.036), and having chronic lung disease (aOR: 3.08; 95%CI: 1.22–7.77, p=0.017) significantly increased the risk of COVID-19 mortality. In contrast, COVID-19 vaccination reduced the risk of COVID-19-associated death. This study highlights that more severe comorbidities, advanced age, and incomplete vaccination were associated with COVID-19 mortality.

Keywords: COVID-19, risk factor, mortality, severity, vaccination

Introduction

The coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is a significant health problem associated with a significant strain on the global economy, civic societies, and healthcare system [1]. While some SARS-CoV-2 infected individuals continue to show no symptoms, others may develop serious respiratory and systemic complications, which can result in multiple organ

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failure and even death [2]. The clinical features of patients with severe COVID-19 have been documented in a number of studies [3,4]. The number and type of risk factors taken into consideration are different in each study.

Age has been identified as the primary predictor of outcomes in COVID-19 patients since the beginning of the epidemic. According to China's early statistics data, the case-fatality rate (CRF) rises sharply beyond the age of 60 and reaches 14.8% for those over the age of 80 [5]. This may be due to the physiological aging process as well as the high incidence of frailty and comorbidities leading to lower functional reserve, impaired intrinsic capacity and resilience, and immune senescence [6]. In addition, the other common risk factors identified were diabetes mellitus (DM), hypertension, chronic kidney disease (CKD), obesity, cardiovascular disease, chronic lung disease, malignancy, liver disease, HIV, male gender, older age, and vaccination status [7-14]. Numerous studies have stated that comorbidities are risk factors for COVID-19 mortality [15-18], but few have considered the severity (spectrum) of the comorbidities. A meta-analysis of seven studies indicated that unvaccinated patients were 2.46 times more likely to die from COVID-19 [17]. Another study found that the mortality rate might drop by 7.6% for every 10% increase in vaccination coverage [19]. However, studies in Indonesia remain limited. The aim of this study was to determine the relationship between the severity of comorbidity, age, and the number of vaccinations received and COVID-19 mortality.

Methods

Study design, setting and sampling

A case-control study was conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, between July 1, 2021, and December 31, 2022, among hospitalized COVID-19 patients. Total sampling was employed in this study. Patients were followed up and further classified into two groups based on mortality status: patients who died and the survivors.

Patients and criteria

This study included hospitalized COVID-19 patients. The diagnosis and clinical severity of COVID-19 at first admission were based on the Guidelines for COVID-19 by the Indonesian Health Ministry [20]. A positive result on the reverse transcriptase-polymerase chain reaction (RT-PCR) assay employing a nasopharyngeal swab was considered to be the COVID-19-confirmed patient [20]. The presence of pneumonia and the severity of COVID were assessed using the diagnosis criteria of the 4th Edition Indonesian Guideline of COVID-19 Management Protocol [21] at hospital admission. Pneumonia was defined as fever, cough, dyspnea/ shortness of breath, tachypnea, or respiratory distress symptoms with radiologic abnormalities on chest x-ray which indicated pneumonia such as infiltrate, reticular opacities, and consolidation on lungs. Mild COVID-19 was considered for asymptomatic patients or patients with mild symptoms such as fever, cough, fatigue, anorexia, anosmia, diarrhea, and vomiting without dehydration. Moderate COVID-19 consists of patients with pneumonia without respiratory distress and a peripheral oxygen saturation of ≥93%. Severe COVID-19 was defined as pneumonia with respiratory distress, decrease of consciousness, convulsion, or the need for an intensive care unit (ICU) for mechanical ventilator or vasopressor support [21]. All severity types of the COVID-19 patients were included in this study. Patients under 18 years old, pregnant women, those who left against medical advice, and those with secondary COVID-19 infections were excluded from the study.

Data collection and study variables

We collected data on age, sex, diagnosis of pneumonia, severity of COVID-19, length of stay, history of COVID-19 vaccinations, presence of comorbidities, and severity of the four most common comorbidities in the study: DM, hypertension, obesity, and CKD. Patients with DM were grouped into three based on their hemoglobin A1c (HbA1c): well-controlled (HbA1c<9%), poorly controlled (HbA1c>9%), and no history of DM [22]. Patients with hypertension were categorized into three categories based on the 2018 European Society of Cardiology (ESC) guidelines [23]: stage 1 hypertension (systolic blood pressure (SBP) of 140–159 mmHg and/or diastolic blood

pressure (DBP) of 90–99 mmHg); stage 2 hypertension (SBP of 160–179 mmHg and/or DBP of 100–109 mmHg); and stage 3 hypertension (SBP of 180 mmHg or greater and/or DBP of 110 mmHg or greater). The body mass index (BMI) classification system from the Indonesian Health Ministry [24] was employed to categorize obesity as follows: normal (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), class 1 obesity (25.0–29.9 kg/m^2), class 2 obesity (≥30.0 kg/m^2), and underweight (18.4–16.4 kg/m^2). Our study defined patients with normal BMI and underweight as "not obese," overweight and class 1 obesity as "mildly obese," and class 2 obesity as "severely obese." CKD patients were grouped based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [25], which classify CKD based on glomerular filtration rate (GFR). These classifications included stage 1 CKD (GFR>90 mL/min per 1.73 m^2), stage 2 CKD (GFR 60–89 mL/min per 1.73 m^2), stage 3 CKD (GFR 30–59 mL/min per 1.73 m^2), CKD stage 4 (GFR 15–29 mL/min per 1.73 m^2), and stage 5 CKD (GFR<15 mL/min per 1.73 m^2 or treatment by dialysis).

COVID-19-associated death was the main outcome determined in this study. The mortality is defined as all-cause mortality of COVID-19 infection.

Statistical analysis

An independent Student's t-test and the Chi-squared test or Mann-Whitney test were employed to assess the associated determinants with COVID-19 mortality according to categorical variables. Significant variables were then further analyzed using multivariate logistic regression with the backward likelihood ratio selection method. Statistical significance was considered at $p<0.05$. All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, USA).

Results

Characteristics of the patients

A total of 1,046 COVID-19-confirmed patients were recruited and followed during the study. We recorded 450 (43%) patients who died and 596 (57%) patients who survived. The patient selection flowchart is depicted in **Figure 1**. The basic characteristics of the COVID-19 patients included in this study are presented in **Table 1**. The majority of patients presented to the hospital with pneumonia (92.5%) at the time of admission and severe COVID-19 symptoms (81.7%). More than half of the patients were unvaccinated (58.4%). Most patients had multiple comorbidities (71.3%), 23.5% had one comorbidity and only 5.3% had no comorbidity. The most common comorbidities were DM (82.7%), CKD (43.0%), hypertension (25.7%), and obesity (23.6%).

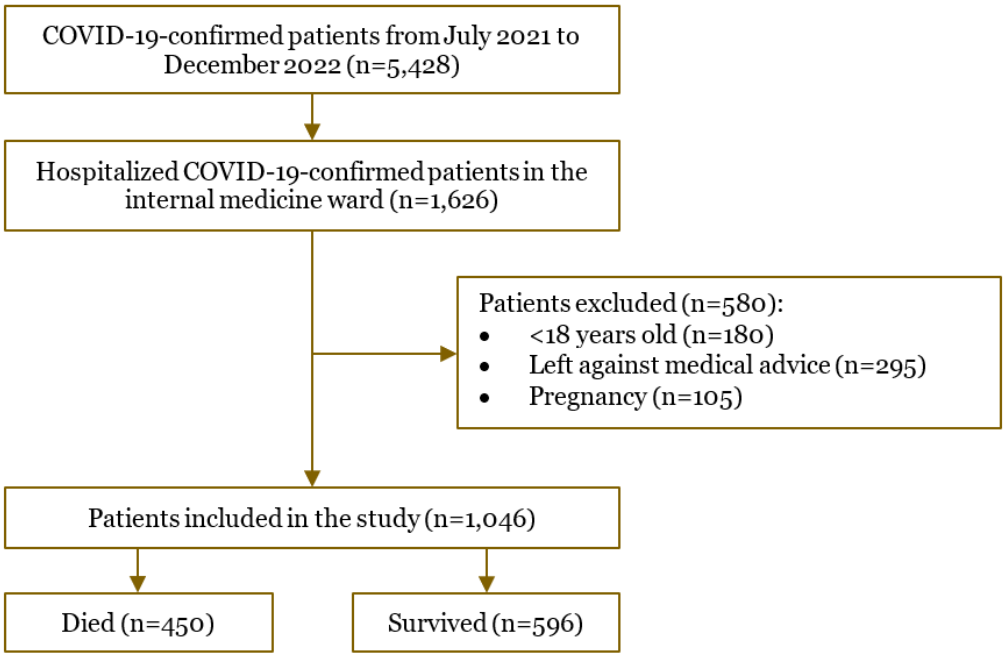

Figure 1. Flowchart of the coronavirus disease 2019 (COVID-19) patient's selection in the study.

Table 1. Characteristics of the COVID-19 patients (n=1,046)

Characteristics	Frequency (%)
Age, mean±SD (years)	51.22±15.05
Sex, n (%)	
Male	560 (53.5)
Female	486 (46.5)
Length of stay, mean±SD (days)	15.44±19.64
Pneumonia	
Present	968 (92.5)
Absent	78 (7.5)
COVID-19 severity	
Mild to moderate	191 (18.3)
Severe	855 (81.7)
Number of COVID-19 vaccines	
0	611 (58.4)
1	104 (9.9)
2	251 (24)
3	78 (7.5)
4	2 (0.2)
Number of comorbidities	
0	55 (5.3)
1	246 (23.5)
2	351 (33.6)
3	273 (26.1)
4	111 (10.6)
5	9 (0.9)
6	1 (0.1)
Comorbidities	
Diabetes mellitus (DM)	865 (82.7)
Hypertension	269 (25.7)
Obesity	247 (23.6)
Chronic kidney disease (CKD)	450 (43.0)
Stroke	45 (4.3)
Coronary artery disease	34 (3.3)
Chronic lung disease	26 (2.5)
Chronic liver disease	42 (4.0)
Malignancy	86 (8.2)
Human immunodeficiency virus (HIV)	46 (4.4)
Autoimmune disease	40 (3.8)
Hematologic disease	25 (2.7)
Mortality	
Died	450 (43.0)
Survived	596 (57.0)

Associations of age, COVID-19 vaccinations, and comorbidities with mortality

Our univariate analysis showed that age (p=0.004), length of stay (p=0.031), the presence of pneumonia (p<0.001), COVID-19 severity (p<0.001), number of COVID-19 vaccinations (p<0.001), DM (p<0.001), hypertension (p<0.001), obesity (p<0.001), CKD (p<0.001), stroke (p=0.046), and chronic lung disease (p=0.026) were associated with mortality (**Table 2**). The mean age in the deceased group was found to be older compared to the surviving groups. The proportion of unvaccinated patients in the deceased group was found to be higher (66.0%) compared to the surviving group (52.7%). The proportion of multiple comorbidities was also found to be higher in the deceased group (89.3%) than in the surviving group (52.7%) (**Table 2**).

Table 2. Factors associated with COVID-19 mortality

Variables	Survived (n=596)	Deceased (n=450)	p-value
Age (years), mean±SD	55.35±11.54	57.78±11.54	0.004 [a*]
Sex, n (%)			
Male	310 (52)	250 (55.6)	0.255 [c]
Female	286 (48)	200 (44.4)	
Length of stay (days), mean±SD	14.21±13.25	17.08±25.697	0.031 [a*]
Pneumonia, n (%)			
Present	518 (86.9)	450 (100.0)	<0.001 [c**]
Absent	78 (13.1)	0 (0.0)	
COVID-19 severity, n (%)			
Mild to moderate	178 (29.9)	13 (6.8)	<0.001 [c**]

Variables	Survived (n=596)	Deceased (n=450)	*p*-value
Severe	418 (70.1)	437 (97.1)	
Number of COVID-19 vaccine, n (%)			
0	314 (52.7)	297 (66.0)	<0.001 [b**]
1	60 (10.1)	44 (9.8)	
2	162 (27.2)	89 (19.8)	
3	58 (9.7)	20 (4.4)	
4	2 (0.3)	0 (0.0)	
Number of comorbidities, n (%)			
0	53 (8.9)	2 (0.4)	<0.001 [b**]
1	200 (33.6)	46 (10.2)	
2	193 (32.4)	158 (35.1)	
3	111 (18.6)	162 (36)	
4	37 (6.2)	74 (16.4)	
5	2 (0.3)	7 (1.6)	
6	0 (0.0)	0 (0.0)	
Comorbidity, n (%)			
Diabetes mellitus (DM)	443 (74.3)	422 (93.8)	<0.001 [c**]
Hypertension	112 (18.8)	157 (34.9)	<0.001 [c**]
Obesity	107 (18)	140 (31.1)	<0.001 [c**]
Chronic kidney disease (CKD)	188 (31.5)	262 (58.2)	<0.001 [c**]
Stroke	19 (3.2)	26 (5.8)	0.046 [c*]
Coronary artery disease	14 (2.3)	20 (4.4)	0.077 [c]
Chronic lung disease	9 (1.5)	17 (3.8)	0.026 [c*]
Chronic liver disease	22 (3.7)	20 (4.4)	0.634 [c]
Malignancy	45 (7.6)	41 (9.1)	0.366 [c]
Human immunodeficiency virus (HIV)	29 (4.9)	17 (3.8)	0.448 [c]
Autoimmune disease	27 (4.5)	13 (2.9)	0.194 [c]
Hematologic disease	19 (3.2)	9 (2.0)	0.254 [c]

[a] Analyzed using independent Student's t-test
[b] Analyzed using Mann-Whitney test
[c] Analyzed using Chi-squared test
[*] Statistically significant at p=0.05
[**] Statistically significant at p=0.001

Multivariate analysis of factors associated with COVID-19 mortality

All significant variables in univariate analysis (age, length of stay, the presence of pneumonia, severity of COVID-19, number of COVID-19 vaccinations, number of comorbidities, and the presence of comorbidities such as DM, hypertension, obesity, CKD, and chronic lung disease) were included in the multivariate analysis. In this analysis, the comorbidities (DM, obesity, hypertension, and CKD) were classified based on their severity (**Table 3**). Variables eliminated from logistic regression using backward likelihood ratio were the length of stay, stroke, and the number of comorbidities.

The analysis showed that the severity of comorbidity was a more significant factor than the number of comorbidities in predicting increased COVID-19 mortality. Older age (aOR: 1.03; 95%CI: 1.02–1.04), poorly controlled DM (aOR: 7.05; 95%CI: 4.63–11.38), stage 2 hypertension (aOR: 1.98; 95%CI: 1.11–3.52), stage 3 hypertension (aOR: 6.59; 95%CI: 2.39–18.17), CKD with GFR≤60 (stage 3, 4, and 5), and chronic lung disease (aOR: 3.08; 95%CI: 1.22–7.77) were associated with COVID-19 mortality (**Table 3**). The number of vaccinations and being female reduced the risk of COVID-19 mortality (**Table 3**).

Table 3. Multivariate logistic regression analysis showing factors associated with mortality

Variables	Multivariate analysis	
	Odds ratio (95%CI)	*p*-value
Age	1.03 (1.02–1.04)	<0.001**
Sex		
Male	Reference	
Female	0.67 (0.50–0.90)	0.007*
Severity of COVID-19 infection		
Mild to moderate	Reference	
Severe	3.13 (2.08–4.73)	<0.001**
Pneumonia		
Present	Reference	
Absent	0.50 (0.30–0.81)	0.005*

Variables	Multivariate analysis	
	Odds ratio (95%CI)	*p*-value
Severity of diabetes mellitus		
Absent	Reference	
Well-controlled (HbA1c<9%)	1.36 (0.97–1.90)	0.072
Poorly controlled (HbA1c≥9%)	7.05 (4.64–11.39)	<0.001**
Severity of obesity		
Absent	Reference	
Mild obesity (BMI 23.0–29.9 kg/m²)	1.14 (0.84–1.55)	0.389
Severe obesity (BMI ≥30 kg/m²)	2.90 (1.72–4.89)	<0.001**
Severity of hypertension		
Absent	Reference	
Stage 1	0.94 (0.62–1.43)	0.792
Stage 2	1.99 (1.12–3.53)	0.019*
Stage 3	6.59 (2.39–18.17)	<0.001**
Severity of chronic kidney disease		
Absent	Reference	
Stage 1	1.43 (0.85–2.42)	0.182
Stage 2	1.40 (0.88–2.22)	0.153
Stage 3	2.5 (1.36–4.59)	0.003*
Stage 4	5.47 (2.18–13.69)	<0.001**
Stage 5	1.71 (1.04–2.81)	0.036*
Chronic lung disease		
Absent	Reference	
Present	3.08 (1.22–7.77)	0.017*
Number of vaccinations		
0	Reference	
1	0.52 (0.32–0.85)	0.009*
2	0.43 (0.31–0.61)	<0.001**
3	0.28 (0.15–0.52)	<0.001**
4	0.00	0.999

BMI: body mass index

Discussion

This study found that hypertension, DM, CKD, and obesity, increased linearly with the stage of disease severity. Two meta-analyses revealed that patients of all ages had an increased chance of critical COVID-19, ICU needs, and mortality outcomes when they had coexisting conditions of DM and hypertension [10,26]. Diabetic and hypertension patients will have decreased resistance to viral infections. Patients with long-term DM and hypertension are more susceptible to developing critical illness in COVID-19 because these conditions can deteriorate cardiac function and damage vascular structure [27]. A study reported an association between higher blood pressure and reduced antibody response to an inactivated viral vaccine (p=0.01) [28]. Other studies found that obesity (BMI≥30 kg/m²) was linked to a worse prognosis and a more severe illness [29,30]. The biological pathways that could be responsible for severe COVID-19 in obese people include inflammation and widely expressed angiotensin-converting enzyme 2 (ACE2) in adipose tissue [31]. A previous study observed the risk of critical COVID-19 as CKD stages progressed [32]. A study compared COVID-19 inpatients with CKD stages 3 and 4 to those without CKD, it was discovered that 12-week mortality odds increased with CKD stage [33]. However, small cohort sizes led to statistically insignificant findings for stage 5 CKD or those on dialysis [33]. Multifactorial pathways are probably responsible for the increasing likelihood of critical COVID-19 related to declining estimated glomerular filtration rate (eGFR). Uremia has been linked to a reduced number of lymphocytes and decreased neutrophil activity in people with end-stage CKD [34].

This study reported that chronic lung disease is a risk factor for COVID-19 mortality. Another study has suggested that there is a greater hospitalization and mortality rate among COPD patients with COVID-19 [7]. This might result from infections in COPD populations, which worsen multi-organ inflammation and cause a delayed recovery of symptoms [35,36].

Age is thought to have an impact on both the risk of COVID-19 mortality and the severity of the illness. Previous studies have shown that the proportion of infections that eventually result in mortality or severe and critical illness increases with age [3,4,37]. According to this study, COVID-19 mortality increased with age. A meta-analysis involving 423,117 patients showed that

older age increased the risk of COVID-19 death (HR 1.31; 95%CI 1.11–1.51) [10]. A different meta-analysis revealed that COVID-19 patients older than 70 years of age seem to be at an increased risk of developing a serious illness, requiring critical care, and passing away [38]. Lower immunity levels and/or age-related chronic medical disorders could be a feasible explanation for this [39]. Furthermore, the functions of B- and T-cells are impacted by aging. A decreased ability to respond effectively to viral infections is linked to a decline in B- and T-cell clonal diversity [40].

According to a study in the United Kingdom on vaccine efficacy, immunization increased protection against serious illness in adults [41]. A prior study found that the death rate might drop by 7.6% for every 10% increase in vaccination coverage [19]. A study carried out after the introduction of the vaccine showed that individuals who were not fully vaccinated had much greater rates of COVID-19 infection, hospitalization, and mortality than those who had received all recommended vaccinations [42]. Similarly, in our study, the mortality risk of COVID-19 was reduced as more vaccinations were received by the patient. According to theory, a successful COVID-19 vaccination can lessen the severity of a SARS-CoV-2 infection-related illness. The growth of immunological memory and the induction of T-cells should also play a role in the protective impact of the vaccination, rather than just the creation of antibodies [43].

There are some limitations of this study. The population only included patients from a single department. A larger population size from other departments for further studies is warranted. Additionally, comorbidities that were classified based on severity only included the four most common comorbidities. Moreover, the CKD population did not differentiate whether patients were on dialysis or not. Furthermore, vaccine types were also not differentiated as homologous or heterologous.

Conclusion

We found that the worsening severity of comorbidities (such as DM, hypertension, CKD, and obesity), older age, chronic lung disease, male, pneumonia occurrence, COVID-19 severity infection at first admission, and incomplete vaccination were increasing the mortality risk of COVID-19 hospitalized patients. Therefore, it is recommended to prioritize these high-risk groups for early intervention and complete vaccination to reduce mortality rates.

Ethics approval

The study was approved by the Dr. Soetomo General Academic Hospital's Ethical Committee (No. 2074/101/4/III/2023).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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