Othman NS, Taufek NHM, Ab Rahman AK, Jamaluddin WA, Zin CS. Patient characteristics and risk factors contributing to mortality among hospitalised patients with COVID-19 in Malaysia. Pharmacy Practice 2023 Jul-Sep;21(3):2857.
https://doi.org/10.18549/PharmPract.2023.3.2857

Original Research

Patient characteristics and risk factors contributing to mortality among hospitalised patients with COVID-19 in Malaysia

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Received (first version): 31-Mar-2023 Accepted: 08-May-2023 Published online: 07-Jul-2023

Abstract

Background: The COVID-19 pandemic caused a significant increase in deaths globally. However, there is a scarcity of data addressing risk factors associated with mortality among hospitalised COVID-19 patients in Malaysia. This study aimed to identify the predictors of death among hospitalised COVID-19 patients in Malaysia. **Methods:** A retrospective cross-sectional study was conducted at two public hospitals in East Coast Malaysia from February 2020 to August 2021. The study included all hospitalised COVID-19 patients by extracting data from the electronic medical records focusing on patient demographics and clinical outcomes. Univariable and multivariable logistic regression analyses were conducted to evaluate association between risk factors and mortality among COVID-19 patients. **Results:** A total of 1060 patients were included (59% male) with median age of 41.5 years (IQR 27 – 58.5). Multivariable logistic regression showed that factors contributing to mortality of COVID-19 patients were elderly (OR, 1.04; 95% CI, 1.02, 1.06; p = 0.001), chronic kidney disease (OR, 3.75; 95% CI, 1.25, 11.27; p = 0.019), an increased point of CCI score (OR, 1.59; 95% CI, 1.25, 2.05; p = ≤0.05), progression to severe stage (OR, 40.68; 95% CI, 17.55, 94.31; p = ≤ 0.05) and admitted to intensive care unit (ICU) (OR, 2.68; 95% CI, 1.16, 6.17, p = 0.021). **Conclusion:** Patients who were elderly, with chronic kidney disease, multiple comorbidities, progressed to severe stage and admitted to ICU were at significantly increased risk of mortality. These findings highlight the importance of implementing extra monitoring and aggressive preventive measures for high-risk patients, in order to reduce their mortality risk and improve patient outcomes.

Keywords: COVID-19; mortality; risk factors; characteristics; Malaysia

INTRODUCTION

The COVID-19 outbreak that started in 2019 has led many countries worldwide to implement multi-faceted preventative and treatment measures to reduce the transmission and fatality rates. Currently, with the availability of newly developed vaccines and medications such as Paxlovid®, many countries are moving towards endemic phase despite the emergence of new COVID-19 variants such as Delta and Omicron.[1,2] These variants have been reported to be more aggressive with higher transmissibility rates which can result in a drastic increase of COVID-19 incidence globally.[3,4]

An individual with COVID-19 infection can be symptomatic or asymptomatic. Fever and cough were commonly reported symptoms while other uncommon symptoms were diarrhea and nausea or vomiting.[5-10] Patients often have mild symptoms in the early course of the disease but may develop to severe symptom; shortness of breath, severe pneumonia and organ failure.[11] Patients who are presented with multiple symptoms such as fever, cough and shortness of breath imply severity of patient illness. A study in Bangladesh has demonstrated that patients who were presented with more than three symptoms had higher risk for mortality.[12] Meanwhile, other studies have found that COVID-19 patients with shortness of breath were significantly associated with severe stage of illness and mortality.[10,13] Thus, the World Health Organization (WHO) recommended patients with shortness of breath and/or oxygen saturation of ≤92% to seek for medical attention and usually would require hospital admission for oxygen support and monitoring.[14]

In Malaysia, the COVID-19 mortality rate has increased by 34.5% in the year 2021 with 166,970 deaths reported compared to those of 2020.[15] This is a significant public health concern that requires immediate attention and preventive measures by all parties especially the community and the government.[16] Early detection and rational allocation of intensive care unit (ICU) resources for severe cases with high risk of poor prognosis upon hospitalization are crucial to reduce mortality and optimize medical resources.[17] There have been a few research that have reported on the risk factors associated with mortality

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www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

among COVID-19 patients in Malaysia. The extent to which underlying diseases and other factors affect mortality among COVID-19 patients has yet to be fully understood. Therefore, this study aimed to determine the risk factors for mortality among hospitalized COVID-19 inpatients in order to optimize valuable healthcare resources and improve patient care.

METHODS

Study designs and setting

This was a retrospective cross-sectional study evaluating patient characteristics and risk factors contributing to mortality among COVID-19 patients during hospitalization. The study was conducted from February 2020 to August 2021 during the pandemic phase, using the medical and prescription database of two public hospitals in East Coast Malaysia, which were Hospital Sultanah Nur Zahirah (HSNZ) Kuala Terengganu and Hospital Hulu Terengganu (HHT). All patients with COVID-19 positive of any age who were admitted to the designated hospitals were included. The study received ethical approval from the Medical Research Ethical Committee, Ministry of Health, Malaysia (NMRR-20-1823-56013). There was no direct involvement of patients in this study, thus written informed consent was not required.

Sample size calculation

Sample size was calculated to ensure the observations in the sample accurately reflect the entire population, allowing for reliable conclusions to be drawn from the results.[18] Sample size in this study was calculated manually by using formula established by Kish (1965).[19] It was based on the estimated 33.8% hospitalization rate of confirmed COVID-19 cases in Malaysia.[20] A confidence level of 99% with a precision of 5% was chosen for the study, resulting in a required sample size of 594 patients to estimate the proportion of hospitalized patients with a 99% confidence interval.

Study variables and outcomes

Patient demographic information such as age, gender, race, smoking status, presenting symptoms upon hospital admission, and comorbidity were included. Among presenting symptoms recorded were fever, cough, sputum, sore throat, runny nose, loss of smell/taste, shortness of breath, diarrhea, fatigue, myalgia, nausea or vomiting, chest discomfort, headache, and loss of appetite. The total number of symptoms per patient was further calculated. Patient characteristics included the presence of following relevant comorbidities: hypertension, diabetes, coronary heart disease, chronic lung disease, chronic kidney disease, and hyperlipidemia. As patients may exhibit more than one comorbidity, Charlson Comorbidity Index (CCI) score was used to calculate the comorbidity score in each patient. The CCI score included 19 comorbidities, with two subcategories of diabetes and liver disease. Each comorbidity was weighted from 1 to 6 and score of comorbidities was sum up to obtain the overall score for mortality risk.[21]

Each COVID-19 patient was classified according to patient's severity of symptoms (stage 1: asymptomatic, stage 2: symptomatic without pneumonia, stage 3: symptomatic with pneumonia, stage 4: symptomatic with pneumonia, requiring supplemental oxygen and stage 5: critically ill with or without organ failures).[22] This study further categorized stage 1 – stage 3 as mild condition, while stage 4 – stage 5 as severe condition. Although most COVID-19 patients had mild condition upon admission, some of them progressed to severe condition during hospitalization. Thus, this study included those patients who progressed from mild to severe stage as well. Data collection process was conducted independently by four research assistants and all data were compiled in a single Microsoft Excel 2020 worksheet according to patient code. Each patient was coded with a unique number to ensure data consistency and accuracy.

Statistical analysis

Data analysis was performed using Stata version 13.1 (StataCorp. 2012. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Descriptive data were presented as frequency and percentage for discrete variables and as mean and standard deviation for continuous variables. Relevant information from STATA were exported to Microsoft Excel to generate graphs.

Logistic regression was performed to analyze the relationships between the outcome measures (independent variables) and outcome (dependent variable).[23] It is one of the most extensively used statistical methods in clinical practice to obtain odds ratio in the presence of more than one explanatory variables (independent variables) on a binary outcome (dependent variable). Logistic regression confers advantage of including continuous variables in the model and does not require specific distributional form for the independent variables. In this study, some data were skewed and deviated from normal distribution which is commonly observed attribution of real data in health, education, and social sciences fields.[23]

To build a logistic model, covariates included must be carefully selected. Chi-square test was conducted to ensure the expected frequency in the contingency tables for each covariate is ≥5. All categorical variables (gender, smoker, comorbidities, progressed to severe stage, ICU admission) included in the regression were ≥5. As for continuous variables, variance inflation factor (VIF) was conducted to test multicollinearity as logistic regression is highly sensitive with high correlation among independent variables.[24] The continuous variables included in this analysis were age, CCI score, and number of symptoms that patients had. A VIF≥1 indicates no correlation between the continuous variables and high VIF ≥10 indicated multicollinearity.[24] The independent variables in this study showed no multicollinearity. Variables with a p-value of ≤0.05 was considered as statistically significant.[25] From univariate analysis, three continuous variables (age, CCI score, and number of symptoms) and seven categorical variables (hypertension, diabetes, coronary heart disease, chronic kidney disease, hyperlipidemia, progressed to severe stage, and ICU admission) met the 0.05 level, thus included in the model for multivariable analysis.

Assessment of goodness of fit (GOF) is important to determine the accuracy of estimated probabilities and to observe how effectively independent variables contribute to the expected outcome. Hosmer-Lemeshow test is one of the statistical tests widely used for goodness of fit for logistic regression model. A small p-value (<0.05) indicates that there is a difference between observed and fitted values which interpret as poor fit model.[26] This study obtained a non-significant p-value, thus indicate the model was an adequate fit.

RESULTS

Patient characteristics

A total of 1060 COVID-19 patients were included in this study and about half of the patients (59%) were male. The median age of the patients was 41.5 years ranging from 0 to 92 years with most of them (32%) aged between 19-39 years. About 94% (n=995/1060) of patients were Malay, followed by 2% (n=22/1060) Chinese, 1% (n=6/1060) Indian and 3% (n=37/1060) were from other ethnic groups. The proportion of smokers were 6% (n=62/1060). Upon admission, majority of patients (n=895/1060 (84%)) were initially categorized as mild in which they were from stage 1 – stage 3. (Figure 1 and 2)

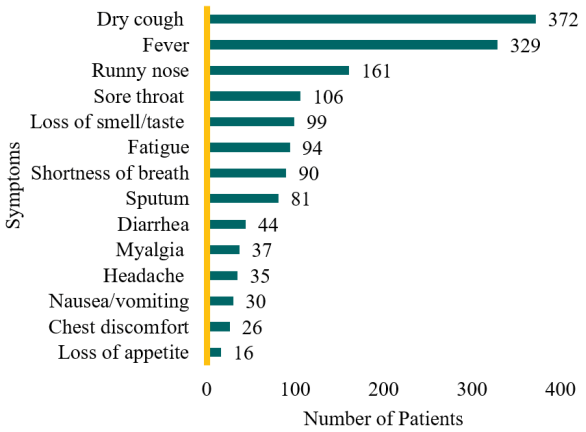

Figure 1. The distribution of symptoms of COVID-19 patients upon hospital admission

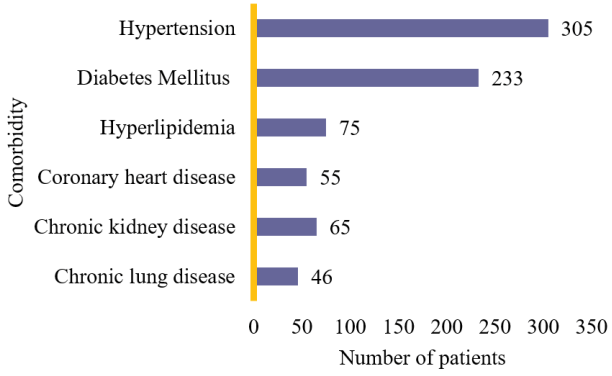

Figure 2. Comorbidity among COVID-19 patients

This study found that dry cough was the main symptom presented in the patients (n=372/1060 (35%)), followed by fever (n=329/1060 (31%)), runny nose (n=161/1060 (15%)), and sore throat (n=106/1060 (10%)). Other less common symptoms included loss of smell/taste (n=99/1060 (9%)), shortness of breath (n=90/1060, (8%)), diarrhea (n=44/1060 (4%)), fatigue (n=94/1060 (9%)), myalgia (n=37/1060 (4%)), nausea or vomiting (n=30/1060 (3%)), chest discomfort (n= 26/1060 (2%)), headache (n=35/1060 (3%)) and loss of appetite (n=16/1060 (2%)).

Thirty eight percent of patients included in this study had comorbidities. Hypertension (n=305) was the most common comorbidities presented, followed by diabetes mellitus (n=233), hyperlipidemia (n=75), chronic kidney disease (n=65), coronary heart disease (n=55), and chronic lung disease (n=46). A large proportion of patients had a charlson comorbidity index sxore of 0, indicating a minimal presence of comorbidities (n=771/1060). This was followed by patients with CCI scores ranging from 1-2 (n= 211/1060), indicating a moderate burden of comorbidities. There were also a smaller number of patients with CCI score ranging from 3-4 (n=55/1060) and those with scores greater than 4 (n=23/1060), indicating a high burden of comorbidites. (Table 1)

Clinical outcome

Out of 1060 patients, 87% (n=923/1060) had been discharged alive and 13% (n=137/1060) died. The median length of

Table 1. Demographic and clinical characteristics of COVID-19 patients

Demographic and Clinical Characteristics	Number of patients (n)	%
Total	*1060*	*100*
Age group, years		
≤12 years	*97*	*9*
13-18 years	*52*	*5*
19-39 years	*343*	*32*
40-59 years	*323*	*30*
≥60 years	*245*	*23*
Gender		
Male	*626*	*59*
Female	*434*	*41*
Ethnicity		
Malay	*995*	*94*
Chinese	*22*	*2*
Indian	*6*	*1*
Others[a]	*37*	*3*
Smoker	*62*	*6*
Case severity upon admission		
Mild	*895*	*84*
Severe	*165*	*16*
Progressed from mild to severe stage during hospitalization	*163*	*15*

[a]Non-Malaysian citizen

hospital stay for all patients was 8 days (IQR 6.0 – 11.0 days). A total of 93 patients (8.8%) were admitted to ICU, of which 38% (n=35/93) were admitted directly from the emergency department (ED) while 62% (n=58/93) were treated in the wards before being transferred to the ICU. Prior to their ICU admission, 97% (n=90/93) patients had progressed from mild to severe stage during hospitalization. The median length of ICU stay was 6 days (IQR 3.0 – 11.0 days). (Table 2)

Table 2. Clinical outcomes of COVID-19 patients

Outcomes	Number of patients (n)	%
Total	*1060*	*100*
ICU admission	*93*	*8.8*
Direct admission from ED	*35*	*38*
Admission after treating in wards	*58*	*62*
Length of ICU stay, days	*6 (IQR 3 – 11)*	
Length of hospital stay, days	*8 (IQR 6 – 11)*	
Discharged alive	*923*	*87*
ICU patients admitted directly from ED	*8*	*23*
ICU patients admitted after treating in wards	*14*	*24*
Death	*137*	*13*
ICU patients admitted directly from ED	*27*	*77*
ICU patients admitted after treating in wards	*44*	*76*

Risk factors associated with mortality

Based on the univariable logistic analysis in our study, there were several factors associated with mortality which were age, hypertension, diabetes mellitus, coronary heart disease, chronic kidney disease, hyperlipidemia, CCI score, number of symptoms, progression from mild to severe stage and admission to ICU. These significant factors were then further regressed using multivariable analysis.

Multivariable logistic regression model showed that an increase of one year in age (OR, 1.04; 95% CI, 1.02: 1.06; p = 0.001) was more likely to cause the mortality. Patients with CKD (OR, 3.75; 95% CI, 1.25: 11.27; p=0.019) were more than three times at higher risk of mortality than those without CKD. In addition, an increase point of CCI score was associated with approximately 1.62 times the risk of mortality (OR, 1.62; 95% CI, 1.27: 2.08; p ≤ 0.05). Patients who progressed from mild to severe stage had about 41 times higher risk of mortality (OR, 40.68; 95% CI 17.55: 94.31; p ≤ 0.05). We also found that ICU admission has doubled the risk of mortality among COVID-19 patients (OR, 2.68; 95% CI 1.16: 6.17; p = 0.021). (Table 3)

DISCUSSION

We report patient characteristics and factors contributing to mortality among hospitalized patients with COVID-19 in the East Coast region in Malaysia. The overall mortality among

Table 3. Univariable and multivariable logistic regression of mortality among COVID-19 patients

Risk factors	Crude OR		P value	Adjusted OR		p value
Age, years*	1.08	(1.07: 1.10)	**≤0.05**	1.04	(1.02: 1.06)	**0.001**
Gender						
Male	0.97	(0.67: 1.39)	0.866			
Female	1					
Smoker						
Yes	1.15	(0.56: 2.40)	0.700			
No	1					
Comorbidities						
Hypertension						
Yes	7.38	(4.98: 10.92)	**≤0.05**	0.96	(0.42: 2.18)	0.919
No	1					
Diabetes mellitus						
Yes	11.43	(7.67: 17.05)	**≤0.05**	1.59	(0.72: 3.53)	0.254
No	1					
Coronary heart disease						
Yes	6.11	(3.46: 10.78)	**≤0.05**	0.38	(0.13: 1.12)	0.080
No	1					
Chronic lung disease						
Yes	1.22	(0.53: 2.79)	0.636			
No	1					
Chronic kidney disease						

Yes	26.26	(14.63: 47.12)	**≤0.05**	3.75	(1.25: 11.27)	**0.019**
No	1					
Hyperlipidemia						
Yes	2.30	(1.31: 4.04)	**0.004**	0.28	(0.10: 0.75)	**0.012**
No	1					
Charlson Comorbidity Index (CCI)	2.22	(1.94: 2.55)	**≤0.05**	1.62	(1.27: 2.08)	**≤0.05**
Number of Symptoms Patient had	1.71	(1.52: 1.91)	**≤0.05**	1.23	(0.99: 1.52)	0.057
Progressed from mild to severe stage						
Yes	158.63	(86.51: 290.89	**≤0.05**	40.68	(17.54:94.31)	**≤0.05**
No	1					
Admitted to ICU						
Yes	42.09	(24.71: 71.70)	**≤0.05**	2.68	(1.16: 6.17)	**0.021**
No	1					

* Per 1 unit increase

patients hospitalized with COVID-19 was 13%. This finding was relatively higher than those previously reported mortality rate (1.2%) during early pandemic in Selangor, Malaysia.[10] The difference is presumably due to emergence of more contagious variants like Delta and Omicron which resulted in drastic increased of COVID-19 cases and hospital admissions during the time of the study. Apart from that, vaccination rate in Terengganu state was lower compared to other state such as Selangor during early pandemic by a difference of 30.5% as of Jun 2021.[27] This may contribute to spread of virus and COVID-19 incidence.

The present study found that elderly emerged as a significant predictor for mortality. The mortality rate for those over 65 years was 65.7% and it was 1.9-fold higher than other age groups. The findings from previous reports were also consistent with the present study in which elderly with COVID-19 was associated with clinical deterioration and poor outcomes.[5,28,29] This may be explained by several factors such as comorbidities, and aging immune system in elderly.[30] Declining function of the third line defense in the body such as T and B lymphocytes and increased inflammatory mediators such as type 2 cytokines concurrently causing chronic inflammation, severe conditions and subsequent death.[31,32]

In this study, COVID-19 patients with comorbidity particularly among elderly group were commonly presented with hypertension and/or diabetes. Nevertheless, a previous study has highlighted that hypertension and diabetes were not significantly associated with mortality, but chronic inflammation, compromised innate immune system and increase coagulation activity among diabetic patients were most likely the cause of severity and mortality.[33] Furthermore, the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) among hypertensive and diabetic patients were questionable during early pandemic. These medications can increase the expression of ACE2 receptors which facilitate the entry of SARS-CoV-2 into the cells, subsequently may increase the risk of developing severity and mortality.[34] However, the latter report maintained the recommendation to continue the use of these medications as there was limited evidence to support the claim to weight benefits and risks.[34,35]

The present study also found that the risk of mortality among patients with chronic kidney disease was 3.72-fold higher than those without chronic kidney disease. This finding was in accordance with international reports that found chronic kidney disease patients with COVID-19 are prone to deteriorating outcomes including mortality.[36-38] The CKD patients are often elderly and had multimorbidity which make them vulnerable to COVID-19 complications. Also, COVID-19 disease can severely affect the already impaired kidney function.[39] Hence, it is imperative to provide special attention and protection of CKD patients to minimize the impact of COVID-19 on their health. Moreover, given that elderly individuals often present with multiple comorbidities, this study assessed the association between CCI score and mortality risk. This study found that every point increase in CCI score added an additional risk of 1.62 times of mortality. This finding is in line with another study by Kuswardhani et al. (2020), which reported a 16% higher risk of mortality for each point increase in the CCI score. The utilization of the CCI score in the context of the COVID-19 pandemic can provide valuable insights into predicting the likelihood of ICU admission, the need for respiratory support and the risk of hospital readmission.[40] Patients with multiple comorbidities are at a higher risk of developing cardiovascular diseases, and it is imperative that they do not hinder or postpone appropriate treatment. This is particularly important for those with COVID-19 and multiple comorbidities, who must adhere to their prescribed treatment to ensure optimal outcomes.[40]

The current study found that 8.8% of hospitalized patients were admitted to the ICU, which was higher than those reported by a previous study (3.3%).[10] This finding suggests that the incidence of critical illness among hospitalized patients may have increased over time, possibly due to a larger number of patients progressing to a severe stage of disease. Furthermore, it could also be due to the change of treatment strategy for patients with hypoxia and policy of early intubation which outlined that hypoxia patients who required oxygen more

than 3L/min should be referred to ICU to prevent catastrophic hypoxic arrest, which likely contributed to the higher ICU admission.[41] The present study also showed that ICU admission was a significant risk factor for mortality among patients with COVID-19, with the odds of 2.68 higher compared to those patients treated in non-ICU. COVID-19 patients associated with ICU admission were also observed to occur more frequently in patients with elderly underlying hyperlipidemia, chronic kidney disease, and patients who admitted with severe stage. Previous studies also found that elderly patients were more likely to be admitted to ICU due to their physiological changes and underlying medical conditions.[42-44]

There are a few limitations of the current study. As this is a cross-sectional retrospective study, the causal effect relationship cannot be established. There was also limited follow-up data for discharged patients who stepped down to COVID-19 Integrated Quarantine and Treatment Center or transferred to other hospitals. Nevertheless, the findings in this study can provide crucial information on early identification and understanding the risk factors for mortality. This will benefit the healthcare and society particularly for healthcare resources allocation such as ICU beds. Additionally, optimal treatment and special attention can be given to the high-risk patients with potential poor outcomes. Identification of risk factors particularly elderly, diabetes, or chronic kidney disease, may guide an early clinical decision making and perform aggressive preventive measures in managing these patients. High-risk patients with COVID-19 infection must report themselves or seek medical consultation at the early stage of disease.

CONCLUSION

In conclusion, factors contributing to high risk of mortality among hospitalized COVID-19 patients were elderly patients, patients who chronic kidney disease, an increase of CCI score, progression from mild to severe stage, and admission to ICU. Identification of high-risk patients provide insight into guiding priorities and resource utilization in implementing proactive management to improve patient outcomes. Future research is needed to better understand the impact of different treatments on the clinical outcomes of COVID-19 patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

CSZ was supported by a Research Grant from the Ministry of Education Malaysia (Fundamental Research Grant Scheme, FRGS/1/2022/SKK16/UIAM/01/3). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGEMENT

The authors would like to thank HSNZ and HHT staffs for their their invaluable assistance in facilitating the data collection process.

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