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PATIENT CHARACTERISTICS AND RISK FACTORS CONTRIBUTING TO DISEASE PROGRESSION AMONG HOSPITALISED PATIENTS WITH COVID-19: LESSON FROM MALAYSIA

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ABSTRACT:

Background: Patients who were hospitalised with severe COVID-19 infection could progress to severe conditions due to various factors, whereas some patients may recover to mild conditions quickly. There was limited information regarding characteristics and factors affecting disease progression in this population in Malaysia. This study aimed to investigate patient characteristics and risk factors contributing to disease progression among COVID-19 patients during hospitalisation.

Methods: A retrospective cross-sectional study using electronic medical record data from COVID-19 patients admitted to two public hospitals in East Coast Malaysia from February 2020 to August 2021 was conducted. This study included patients with asymptomatic or mild condition (stage 1 – stage 3) upon hospital admission and progressed to severe condition (stage 4 – stage 5) during hospitalisation.

Results: A total of 163 patients were included (57% male) with the age of (mean±SD, 62.3 ±14.0 years). Multivariable logistic regression associated with COVID-19 disease progression included elderly (OR, 1.06; 95% CI, 1.04, 1.08; p = ≤0.05), diabetes mellitus (OR, 2.27; 95% CI, 1.27, 4.06; p = 0.006), chronic kidney disease (OR, 4.87; 95% CI, 1.92, 12.38; p=0.001), and presented with more than three COVID-19 symptoms (OR, 9.80; 95% CI, 6.08-15.81, p = ≤0.05).

Conclusion: Risk factors for COVID-19 disease progression included elderly patients, comorbidities of diabetes mellitus, chronic kidney disease or more than three COVID-19 symptoms. Close monitoring and early intervention should be implemented for these patients to prevent the disease progression and poor prognosis.

KEYWORDS: *COVID-19, disease progression, risk factors, patient characteristics, Malaysia*

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1. INTRODUCTION

The coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) [1]. As of 11th April 2022, rapid transmission of this virus has caused 499 million COVID-19 cases with 6 million deaths worldwide [2]. Most COVID-19 patients were asymptomatic or having mild symptoms such as fever and cough and commonly have a good prognosis without needing specific treatment [3]. Generally, less than 50% of patients had a fever upon hospital admission, but over the course of disease, majority of patients (89%) had fever during the hospitalisation [4]. However, COVID-19 infection is aggressive that it can worsen the condition of infected patients rapidly. Some patients including the elderly and those with medical conditions are hospitalised for having deteriorated condition or at high risk of developing severe illness. Previous reports from China, New York and Italy showed that majority hospitalised patients were among elderly and/or with underlying comorbidities such as hypertension and diabetes. In severe cases, these patients developed shortness of breath, hypoxia and progressed to critical conditions such as acute respiratory distress syndrome (ARDS), acute respiratory failure, and septic shock [3]. Previous findings in Malaysia reported that those who developed complications were among patients who were initially diagnosed with severe and critical-stage COVID-19 [5].

In addition, some patients who progressed to a severe stage were commonly admitted to the intensive care unit (ICU) for close monitoring and treatment, whereas some of them died before ICU admission. As of 22nd May 2022, there were about 6 million reported deaths due to COVID-19 globally. Reported mortality rates were varied across the countries. Mortality analyses demonstrated that the upper middle-income countries such as South Africa, Brazil and Guatemala had higher mortality rate compared to high income countries such as Japan, France, and Portugal [7]. The differences in mortality rates could be due to the variation in the size and demographics of the tested populations, and their quality of healthcare system [7]. A recent systematic review reported that elderly, male, current smoker, and chronic comorbidities were significantly associated with mortality [8]. However, risk factors contributing to disease progression were not well-explored particularly in Malaysia. Hence, this study aimed to investigate characteristics and risk factors of patients who progressed from mild to severe stage to facilitate early detection and guide the physicians or clinicians to decide the best treatment plan and preventive measures for these patients.

2. METHODOLOGY

This was a retrospective cross-sectional study evaluating patient characteristics and risk factors contributing to disease progression among COVID-19 patients during hospitalisation. The study was conducted from February 2020 to August 2021 using the medical and prescription database of two public hospitals in East Coast Malaysia, Hospital Sultanah Nur Zahirah (HSNZ) Kuala Terengganu and Hospital Hulu Terengganu (HHT). 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 in this study was calculated manually by using formula derived from Kish (1965) [5]. It was based on the estimated prevalence of hospitalised patients among confirmed cases of COVID-19 in Malaysia who progressed from mild to severe stage, which was about

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3.5% [6]. Confidence level in this study was set at 99% with 5% precision. The required sample size for estimation of proportion of hospitalised patients with 99% confidence interval was 90 patients.

COVID-19 severity was categorised into four stages (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) depending on patients' severity of symptoms [9]. This study included COVID-19 patients diagnosed with the asymptomatic or mild conditions (stage 1 – stage 3) upon hospital admission and progressed to severe condition (stage 4 – stage 5) during hospitalisation. Information extracted from the database included patient demographics; age, gender, smoking status, presenting COVID-19 symptoms, comorbidities, disease staging upon hospital admission and hospitalisation, and patient outcomes; number of patients admitted to ICU, length of hospital stay, and discharged alive or death. All extracted data was computed into Microsoft Excel 2020 and each patient was coded with a unique number to ensure data consistency. Data collection process was conducted independently by four research assistants and all data were compiled together in a single Excel worksheet according to patient code. In this study, age was categorized into 19-39 years, 40-59 years and ≥60 years [36]. Total number of COVID-19 symptoms per patient was calculated and further categorised into more than or equal to three symptoms and less than three symptoms. Meanwhile, comorbidities included were hypertension, diabetes mellitus, coronary heart disease, chronic obstructive lung disease, chronic kidney disease, and hyperlipidemia. As patients commonly presented with more than one comorbidity, Charlson Comorbidity Index (CCI) score was computed to calculate the comorbidity score in each patient.

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. Graph presentations were plotted using Microsoft Excel. Relevant information from STATA was exported to Excel to generate the graph. Multivariable logistic regression was used to analyze the associations between patient demographics and COVID-19 progression. Reported p values ≤0.05 were considered statistically significant.

3. RESULT

3.1. Patient characteristics

A total of 163 COVID-19 patients who progressed from mild to severe stage were included in this study and about half of the patients (57%) were male. The mean age of total patients was 62.3 ± 14.0. Patients who aged more than 60 years recorded the highest proportion (62%), followed by 40-59 years (30%) and 19-39 years (8%). Few of them were smokers (8%).

Sixty-seven percent of patients included have comorbidities and majority had CCI score of 1-2 (44%). Hypertension (n=110) was the most common comorbidity presented, followed by diabetes mellitus (n=101), and chronic kidney disease (n=46).

Upon hospital admission, dry cough (n=106) was the main symptom predominantly presented among progressed COVID-19 patients, followed by fever (n=95) and fatigue (n=69). Other less common symptoms included shortness of breath (n=60), sputum (n=35), runny nose

(n=18), diarrhea (n=18), loss of smell/taste (n=14), myalgia (n=10), nausea/vomiting (n=10), chest discomfort (n=8), loss of appetite (n=7), sore throat (n=4), and headache (n=3). Overall, majority presented with ≥3 number of COVID-19 symptoms (64%).

Table 1: Patient demographic and clinical characteristics of patients progressed from mild to severe stage during hospitalisation

Baseline Characteristics	Number of patients (n)	%
Age group, years		
19-39 years	13	8
40-59 years	49	30
≥60 years	101	62
Gender		
Male	93	57
Female	70	43
Smoker	13	8

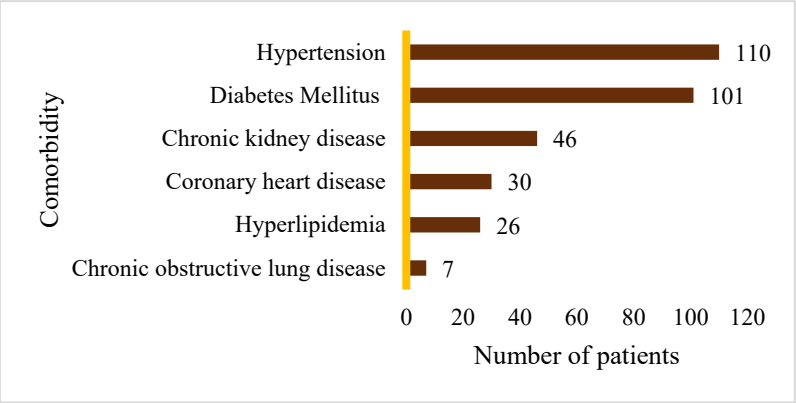

Fig. 1. Comorbidity among patients who progressed from mild to severe stage

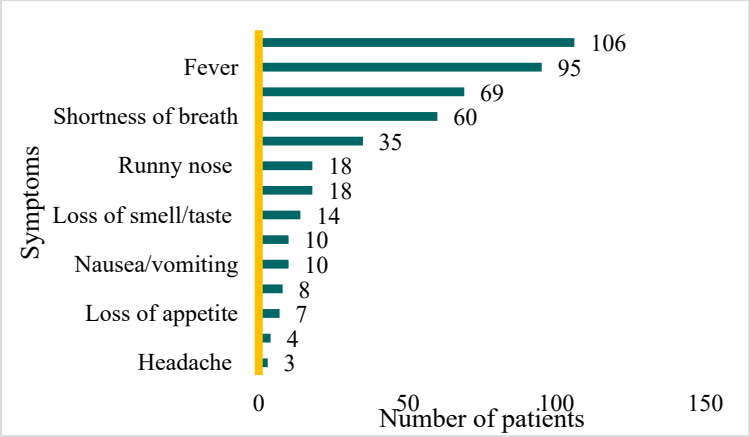

Fig. 2. The distribution of symptoms upon hospital admission among patients progressed from mild to severe stage

3.2. COVID-19 complications

Fifty-nine percent (n=96/163) patients who progressed from mild to severe stage had complication of COVID-19 infection. Acute kidney injury was the most frequently observed complication, followed by multiorgan failure and septicemic shock. For lung complications, only a few developed respiratory failures (2%) and acute respiratory distress syndrome (1%). Majority of them had only one COVID-19 complication (n=44), whereas others had two (n=28) or three complications (n=19).

Table 2: Complications of progressed COVID-19 patients

COVID-19 Complications	Total (n=163)
Acute kidney injury	36
Multiorgan failure	35
Septicemic shock	27
Acidosis	26
Secondary infection	18
Respiratory failure	14
Acute respiratory distress syndrome	13
Sepsis	7
Heart failure	1
Coagulopathy	1

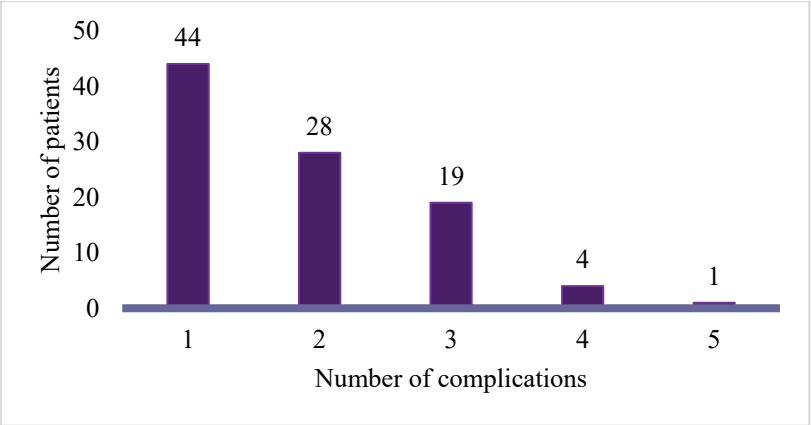

Fig. 3. Number of complications among progressed COVID-19 patients

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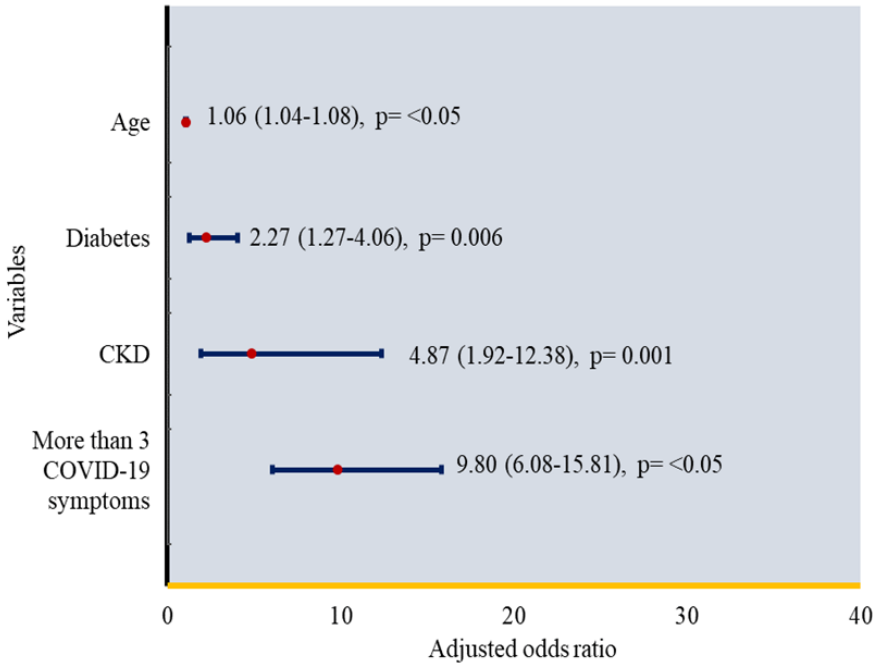
3.3. Clinical outcomes

Out of the 163 patients, 55% of them were admitted to ICU (n=90). The mean ± standard deviation for length of hospital stay was 11 ± 9.7 days. Among these patients, 74% died and 26% discharged alive.

3.4. Risk factors associated with disease progression

In univariable logistic analysis, there were significant associations between disease progression and specific underlying factors including age, hypertension, diabetes mellitus, coronary heart disease, chronic kidney disease, hyperlipidemia, CCI score, and more than or equal to 3 symptoms presented. The odds of disease progression to severe stage among COVID-19 patients for elderly was 8% higher than non-elderly patients (OR, 1.08, 95% CI 1.06-1.09, p = ≤0.05). Patients presented with hypertension, diabetes mellitus, coronary heart disease, chronic kidney disease or hyperlipidemia were 7.37, 9.61, 7.94, 18.35 and 3.09 times more likely to progress to severe stage, respectively. In addition, the higher the CCI score, the higher the odds of disease progression (OR 1.97, 95% CI 1.74-2.24, p = ≤ 0.05). Patient presented with more than 3 COVID-19 symptoms were significantly associated with disease progression (OR 7.83, 95% CI 5.45-11.26, p = ≤0.05).

Multivariable logistic regression model showed that only age (OR, 1.06; 95% CI, 1.04, 1.08; p = ≤0.05), diabetes mellitus (OR, 2.27; 95% CI, 1.27, 4.06; p = 0.006), chronic kidney disease (OR, 4.87; 95% CI, 1.92, 12.38; p=0.001), and presented with more than 3 COVID-19 symptoms (OR, 9.80; 95% CI, 6.08-15.81, p = ≤0.05) were remained to be significantly associated with COVID-19 progression.



CKD = chronic kidney disease

Fig. 4. Multivariable logistic regression of risk factors for COVID-19 progression

Table 3: Univariable and multivariable logistic regression of disease progression among COVID-19 patients

Risk factors	Crude OR		P value	Adjusted OR		p value
Age, years	1.08	(1.06, 1.09)	**≤0.05**	1.06	(1.04, 1.08)	**≤0.05**
Gender						
Male	1.12	(0.80, 1.57)	0.524			
Female	1					
Smoker						
Yes	1.51	(0.80-2.85)	0.203			
No	1					
Comorbidities						
Hypertension						
Yes	7.37	(5.12, 10.60)	**≤0.05**	1.17	(0.68, 2.03)	0.566
No	1					
Diabetes mellitus						
Yes	9.61	(6.65, 13.88)	**≤0.05**	2.27	(1.27, 4.06)	**0.006**
No	1					
Coronary heart disease						
Yes	7.94	(4.53, 13.91)	**≤0.05**	1.43	(0.65, 3.14)	0.370
No	1					
Chronic lung disease						
Yes	0.99	(0.44, 2.26)	0.990			
No	1					
Chronic kidney disease						
Yes	18.35	(10.39, 32.39)	**≤0.05**	4.87	(1.92, 12.38)	**0.001**
No	1					
Hyperlipidemia						
Yes	3.09	(1.85, 5.17)	**≤0.05**	0.81	(0.41, 1.59)	0.541
No	1					
Charlson Comorbidity Index (CCI)	1.97	(1.74, 2.24-)	**≤0.05**	1.19	(0.96, 1.48)	0.118
Number of Symptoms Presented						
≥3 symptoms	7.83	(5.45, 11.26)	**≤0.05**	9.80	(6.08,15.81)	**≤0.05**
<3 symptoms	1					

4. DISCUSSION

This study found that elderly patients (≥60 years), patients who had diabetes, chronic kidney disease, and patients presented with three or more COVID-19 symptoms had high risk for disease progression from mild to severe stage [36]. Fifty percent of those progressed to a severe stage have also developed COVID-19 complications with acute kidney injury and multiorgan failure being the most common complications. This is in accordance with findings

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from previous study which reported acute kidney injury as a common COVID-19 complication [6]. Nevertheless, COVID-19 is a multi-system disease that can cause multiple complications involving renal, respiratory, cardiovascular, neurological and gastrointestinal system [11].

The current study observed that age was a significant predictor for progressing from mild to severe disease by 1.06. This corresponds to the recent study conducted in the United States which found that advanced age emerged as risk factor for severe COVID-19 disease [12]. This can be attributed by the presence of multiple comorbidities, and deteriorating immune system among elderly [13]. Elderly patients are often associated with declining function of antigen-specific immune responses such as T and B lymphocytes and increased inflammatory mediators such as type 2 cytokines which cause prolonged inflammation and eventually severe conditions [14]. Declining immune function may reduce vaccine efficacy, decrease in immune surveillance and increase susceptibility to infections [13].

In addition, our study showed that the common symptoms that patients had included dry cough and fever. Patients who presented with three or more symptoms upon hospital admission appeared to be a significant factor of severe disease. A retrospective cohort study in Bangladesh also found a significant association between > 3 symptoms and mortality [15]. Our findings were also in line with previous studies which highlighted that fever and dry cough were the most common symptoms presented upon hospital admission [16-19]. It is highly likely that presenting with many COVID-19 symptoms such as fever, cough and shortness of breath imply severity of patient illness and affect quality of life. Hence, medical treatment and monitoring should be given immediately to control the intensity of illness and to prevent the COVID-19 progression to a severe state.

Our study indicated that higher number of male patients with COVID-19 were admitted to the hospital compared to females. However, gender was not significantly associated with disease progression and this finding is similar to a previous study conducted in Malaysia [6]. Other studies demonstrated that male patients had higher hospitalisation and mortality rate compared to female patients [20-21]. In contrast, a meta-analysis has emphasised male patients have been associated with adverse outcomes of COVID-19 in terms of high risk of severe disease and death [22]. This may be explained by the fundamental differences such as males have higher ACE2 expression, inferior immune response, and unhealthy lifestyle behavior, i.e., drinking alcohol and smoking compared to females [22]. Furthermore, females have higher number of CD4+ T cells, CD8+ T cells and B cell production than males which affect the ability to fight the COVID-19 infection [22]. Apart from that, females have more responsible attitude towards COVID-19 pandemic in which males have lacking self-awareness and undertaking preventive measures such as wearing mask, frequent hand wash and social distancing [23].

Another factor that is commonly associated with the severity among COVID-19 patients is smoking. Our study showed that the prevalence of smokers among patients with COVID-19 (8%) was slightly lower than a recent study conducted in Malaysia (9%) [6] probably due to smaller sample size. It has been reported that smoking was not significantly associated with severe disease [24-25]. However, a meta-analysis study has reported that smokers were among COVID-19 patients with increased risk for severe disease [26] and mortality [27]. In general, smoking is harmful in all patients as it weakens the immune system and susceptible to viral and bacterial infection [24].

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The present study also found that the risk of patients with chronic kidney disease was 4.87-fold higher to develop severe COVID-19 than those without chronic kidney disease. This finding is supported by previous studies that showed chronic kidney disease patients with COVID-19 are prone to deteriorating outcomes including mortality [28-29]. In addition, Soares et al. (2020) have reported that COVID-19 patients with CKD have high risk of developing serious infection [17]. Furthermore, acute kidney injury is a common incidence in patients with chronic kidney disease [30]. This increases the risk of severity of COVID-19 disease and eventually resulted in a poor prognosis [30].

There are several explanations why chronic kidney disease increased the risk progression to severe disease. Physiologically, patients with chronic kidney disease have increased expression of ACE2 receptor in tubular cells. This enhances the binding of SARS-COV-2 towards the ACE2 receptor which eventually induce cytotoxicity and abnormal renal function [10]. Hence, both decreased kidney function and severe COVID-19 condition may deteriorate the patient's health to critical condition or death. Similarly in elderly patients, CKD is associated with decreased function of immune system such as monocyte, neutrophil phagocytosis, T-lymphocytes, and B lymphocytes [31]. These mechanisms may explain the high risk of disease progression among COVID-19 patients with CKD particularly in elderly patients as shown in the current study.

Other comorbidities that were measured by Charlson Comorbidity Index (CCI) in the current study showed that an increase in one CCI score was significantly associated with poor outcomes in COVID-19 patients in univariable analysis. This is consistent with another study by Kuswardhani et al. (2020) which found that an increase in CCI score has increased the risk of mortality by 16% [32]. Some studies have also reported on the significant association between hypertension and diabetes mellitus with the severity and mortality in COVID-19 patients [24, 33-34]. Although hypertension was the most common comorbidity among COVID-19 patients in the present study, it did not significantly associate with disease severity and mortality. This difference compared to other studies could be due to different variables in study population such as age and underlying medical conditions. On the other hand, diabetes was significantly associated with COVID-19 severity. The potential mechanism by which COVID-19 infection increases the risk for severe disease among diabetic patients was similar to chronic kidney disease. Among the mechanisms are increased in viral entry, decreased viral clearance, compromised immune system, hyperinflammation and cytokine storm [34].

The overall mortality rate among patients who progressed from mild to severe stage in the current study was 74%. This rate was higher compared to previous studies (15% - 8.3%) [6, 24]. This is probably due to the current study focused on those who progressed to the severe stage during hospitalisation while previous studies considered severe patients upon hospital admission. Therefore, some severe patients in previous studies may de-escalate to mild stage during hospitalisation which lower the mortality rate. Furthermore, higher mortality rate in the current study could be due to difference in the period of data collection whether it was in the early or later phase of pandemic. The later phase was associated with the emergence of more contagious Delta variant that has caused higher number of hospital admissions than earlier variants. During the data collection period of the current study, the COVID-19 vaccination rate in Terengganu particularly in Kuala Terengganu and Hulu Terengganu was low compared to other states that may contribute to the slightly higher mortality in the current study [35].

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The findings in the present study will redound to healthcare and society's benefits as early identification and understanding the patient risk factors provide crucial information for healthcare resources allocation particularly the ICU beds. It emphasizes the knowledge about high-risk patients with poor prognosis. Patients who are at high risk should be given special attention even though they are diagnosed with mild stage upon hospital admission. They may develop severe condition during hospitalisation and eventually lead to the worst outcomes. However, a causal effect relationship cannot be established in this study due to limitation of a retrospective cross-sectional design. Nevertheless, this real-world data will be able to provide real-world evidence, which is important to optimize the valuable healthcare resources as well as to improve patient care. Identification of risk factors particularly elderly, diabetes, or chronic kidney disease, may guide an early clinical decision making in managing these patients. High-risk patients with COVID-19 infection must report themselves or seek medical consultation at early stage of disease. This also alerts the physicians or clinicians to perform aggressive preventive measures for these patients.

5. CONCLUSION

In conclusion, this study found that elderly patients, patients who had diabetes, chronic kidney disease, and presented with ≥3 symptoms of COVID-19 have a high risk to progress from mild to severe stage. Early identification of high-risk patients may provide insight into the clinical and policy guidelines in prioritization of pharmaceutical interventions and stratification for high-risk COVID-19 patients who are associated with poor outcomes. Furthermore, it will also guide the priorities and utilization of resources in implementing aggressive management to improve the patient outcomes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

[1] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD. (2021). Features, Evaluation, and Treatment of Coronavirus (COVID-19). Treasure Island (FL): StatPearls Publishing. Available from https://www.ncbi.nlm.nih.gov/books/NBK554776/

[2] Elflein J. (2021). Coronavirus (COVID-19) disease pandemic – statistics and facts. Statista. https://www.statista.com/topics/5994/the-coronavirus-disease-covid-19-outbreak/

[3] Choi MH, Ahn H, Ryu HS, Kim B, Jang J, Jung M, Kim J, Jeong SH. (2020). Clinical characteristics and disease progression in early-stage COVID-19 patients in South Korea. Journal of Clinical Medicine, 9(6):1959. https://doi.org/10.3390%2Fjcm9061959

[4] Centers for Disease Control and Prevention. (2021, February 12). Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

[5] Daniel, WW. (2005). Biostatistics: A foundation for analysis in the health sciences. John Wiley & Sons, Inc.

[6] Sim BLH, Chidambaram SK, Wong XC, Panthmanathan, MD, Peariasamy KM, Hor CP, … Goh PP. (2020). Clinical characteristics and risk factors for severe COVID-19 infection. The Lancet Regional Health – Western Pacific 4. https://doi.org/10.1016/j.lanwpc.2020.100055

[7] Johns Hopkins University & Medicine. (2022). Mortality analyses. https://coronavirus.jhu.edu/data/mortality

[8] Dessie ZG, Zewotir T. (2021). Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423117 patients. BioMed Central (BMC) Infectious Diseases, 21: 855. https://doi.org/10.1186%2Fs12879-021-06536-3

[9] Ministry of Health Malaysia. (2020). Annex 2e: Clinical management of confirmed COVID-19 case in adult and paediatric. Retrieved from http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_2e_Clinical_Management_For_Confirmed_COVID-19_in_Adult_and_Paed.28.09.20.pdf

[10] Fan C, Lu W, Li K, Ding Y, Wang J. (2021). ACE2 expression in kidney and testis may cause kidney and testis infection in COVID-19 patients. Frontiers in Medicine, 7, 563893. https://doi.org/10.3389/fmed.2020.563893

[11] John KJ, Nayar J, Mishra AK, Selvaraj V, Khan MS, Lal A. (2021). In-hospital clinical complications of COVID-19: a brief overview. Future Virol. https://doi.org/10.2217%2Ffvl-2021-0200

[12] Hobbs ALV, Turner N, Omer I, Walker MK, Beaulieu RM, Sheikh M, Spires SS, Fiske CT, Dare R, Goorha S, Thapa P, Gnann J, Wright J, Nelson GE. (2021). Risk factors for mortality and progression to severe COVID-19 disease in the Southeast region in the United States: A report from SEUS Study group. Infection Control & Hospital Epidemiology, 42(12), 1464-1472. doi:10.1017/ice.2020.1435

[13] Damayanthi H, Prabani K, Weerasekara I. (2021). Factors associated for mortality of older people with COVID-19: A systematic review and meta-analysis. Gerontology & geriatric medicine, 7, 23337214211057392. https://doi.org/10.1177/23337214211057392

[14] Ponnappan S, Ponnappan U. (2011). Aging and immune function: molecular mechanisms to interventions. Antioxidants & redox signaling, 14(8), 1551–1585. https://doi.org/10.1089/ars.2010.3228

[15] Sharif N, Opu RR, Ahmed SN, Sarkar MK, Jaheen R, Daullah MU, … Talukder AA. (2021). Prevalence and impact of comorbidities on disease prognosis among patients with COVID-19 in Bangladesh: a nationwide study amid the second wave. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 102148. https://doi.org/10.1016/j.dsx.2021.05.021

[16] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. The Lancet, 395(10223), 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

[17] Soares RCM, Mattos LR, Raposo LM. (2020). Risk factors for hospitalisation and mortality due to COVID-19 in Espirito Santo State, Brazil. The American Journal of Tropical Medicine and Hygiene, 103(3): 1184-1190. 10.4269/ajtmh.20-0483.

[18] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, … Song Y. (2020). Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. Journal of the American Medical Association (JAMA) Internal Medicine, 180(7):934–943. doi:10.1001/jamainternmed.2020.0994

[19] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang Li. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. The Lancet, 395(10223), 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7m

[20] Dessie ZG, Zewotir T. (2021). Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423117 patients. BioMed Central (BMC) Infectious Diseases, 21: 855. https://doi.org/10.1186%2Fs12879-021-06536-3

[21] Nguyen NT, Chinn J, Ferrante MD, Kirby KA, Hohmann SF, Amin A. (2021). Male gender is a predictor of higher mortality in hospitalised adults with COVID-19. Plos one, 16(7): e0254066. https://doi.org/10.1371/journal.pone.0254066

[22] Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, Rosser EC, Webb K, Deakin CT. (2020). Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nature Communications, 11, 6317. https://doi.org/10.1038/s41467-020-19741-6

[23] Bwire, G. M. (2020). Coronavirus: why men are more vulnerable to COVID-19 than women? Springer Nature Comprehensive Clinical medicine, 2 (7): 874-876. https://dx.doi.org/10.1007%2Fs42399-020-00341-w

[24] Ismail SNA, Zaki IAH, Noordin ZM, Hussin NSM, Ming LC, Zulkifly HH. (2022). Clinical characteristics and risk factors for mortality in patients with COVID-19: A retrospective nationwide study in Malaysia. Proceedings of Singapore Healthcare, 1-8. https://doi.org/10.1177%2F20101058221085743

[25] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, … Cao B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet, 395(10229), 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3

[26] He X, Lau EHY, Wu P. Deng X, Wang J, Hao X, Lau YC, Wong, JY, Guan Y, Tan X, Mo X, Chen Y, Liao B, Chen W, Hu F, Zhang Q, Zhong M, Wu Y, Zhao L, Zhang F, Cowling BJ, Li F, Leung GM. (2020). Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature Medicine, 26, 672–675. https://doi.org/10.1038/s41591-020-0869-5

[27] Salah HM, Sharma T, Mehta J. (2020). Smoking doubles the mortality risk in COVID-19: A meta-analysis of recent reports and potential mechanisms. Cureus, 12(10), e10837. https://doi.org/10.7759%2Fcureus.10837

[28] Rastad H, Ejtahed H, Shafiee G, Safari A, Shahrestanaki E, Khodaparast Z, … Qorbani M. (2021). The risk factors associated with COVID-19-related death among patients with end-stage renal disease. BMC Nephrology, 22, 33. https://doi.org/10.1186/s12882-020-02221-w

[29] Menon T, Gandhi SAQ, Tariq W, Sharma R, Sardar S, Arshad AM, Adhikari R, Ata F, Kataria S, Singh R. (2021). Impact of chronic kidney disease on severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Cureus, 13(4): e14279. https://doi.org/10.7759/cureus.14279

[30] Sabaghian T, Kharazmi AB, Ansari A, Omidi F, Kazemi SN, Hajikhani B, Vaziri-Harami R, Tajbakhsh A, Omidi S, Haddadi S, Bonjar AHS, Nasiri MJ, Mirsaridi M. (2022). COVID-19 and acute kidney injury: a systematic review. Frontiers in Medicine, 9:705908. https://doi.org/10.3389/fmed.2022.705908

[31] Chou C, Wang S, Liang C, Chang C, Liu J, Wang I, Hsiao L, Muo C, Huang C, Wang R. (2014). Risk of pneumonia among patients with chronic kidney disease in outpatient and inpatient settings: a nationwide population-based study. Medicine (Baltimore), 93(27): e174. https://doi.org/10.1097/md.0000000000000174

[32] Kuswardhani RAT, Henrina H, Pranata R, Lim MA, Lawrensia S, Suastika K. (2020). Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 2103-2109. https://doi.org/10.1016/j.dsx.2020.10.022

[33] Saleh MA, Alotaibi N, Schrapp K, Alsaber A, Pan J, Almutairi F, ... Alroomi M. (2022). Risk factors for mortality in patients with COVID-19: The Kuwait Experience. Medical Principals and Practice, 117, 1–7. doi: 10.1159/000522166

[34] Almeida-Pititto B, Dualib PM, Zajdenverg L, Dantas JR, Souza FD, Rodacki M, Bertoluci MC, Brazillian Diabetes Society Study Group. (2020). Severity and mortality of COVID-19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. Diabetology & Metabolic Syndrome, 12:75. https://doi.org/10.1186/s13098-020-00586-4

[35] Ministry of Health Malaysia. (2022). COVIDNOW in Malaysia. Retrieved from https://covidnow.moh.gov.my/

[36] World Health Organization. (2022). Ageing and health. Retrieved from https://www.who.int/news-room/fact-sheets/detail/ageing-and-health#:~:text=By%202030%2C%201%20in%206,will%20double%20(2.1%20billion).