

Original Article:**Predictive factors for severe COVID-19 infection in Terengganu state of Malaysia.**

Hafizuddin Awang¹, Mohd Hanief Ahmad², Kamarul Azhar Mohamed², Azmani Wahab³, Norafidah Abdul Rashid³, Hasnan Arwit³, Mohd Anuar Abd Rahman³, Kasemani Embong³

Abstract

Background: COVID-19 has a varied clinical presentation and may progress to severe form which could be fatal. Determination of risk factors for severe infection would be beneficial in averting COVID-19 mortality in Terengganu setting. **Materials and Methods:** A case-control study between mild and severe COVID-19 groups was conducted in Terengganu state from 1st March 2020 until 31st January 2021 based on retrospective record review. Individuals with laboratory RT-PCR confirmed positive test for COVID-19 were included as study samples. Descriptive statistics, simple and multiple logistic regression analyses were employed for statistical analysis. **Results:** There were 2142 COVID-19 cases in Terengganu during the studied period. The proportion of severe COVID-19 infection was 2.1% (95%CI: 0.01, 0.03). Among the severe COVID-19 cases, their mean ($\pm$ SD) age was 52 ($\pm$ 16) and majority of them were male (59.1%) and had comorbidity (56.8%). The common symptoms among severe COVID-19 cases included fever (68.2%), cough (63.6%), coryza (22.7%), sore throat (13.6%) and anosmia (11.4%). Multiple logistic regression revealed older age, presence of comorbidity, having symptoms of fever, cough and anosmia as the significant associated factors for severe COVID-19 with adjusted odds ratio (AOR) of 1.07 (95%CI: 1.03, 1.11), $p < 0.001$; AOR 5.97 (95%CI: 2.09, 17.01), $p = 0.001$; AOR 4.78 (95%CI: 1.63, 14.05), $p = 0.004$; AOR 4.81 (95%CI: 1.70, 13.60), $p = 0.003$; and AOR 8.39 (95%CI: 1.39, 50.33), $p = 0.020$, respectively. **Conclusion:** Knowing the predictive factors for severe COVID-19 would facilitate clinicians in timely identification of high-risk cases for delivering prompt treatment and intervention.

Keywords: COVID-19, severe infection, fever, comorbidity, Malaysia.

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Introduction

The current pandemic of coronavirus disease 2019 (COVID-19) particularly during the mitigation phase had triggered public health physicians and clinicians to identify population at greatest risk of developing severe form of COVID-19 to avert mortality. In Malaysia, every COVID-19 case will be stratified according to clinical stage of severity which include stage I (asymptomatic); stage II (symptomatic without pneumonia); stage III (pneumonia without hypoxia); stage IV (hypoxic

pneumonia which requires supplemental oxygen); and stage V (critically ill and requires mechanical ventilation)¹. The course of COVID-19 illness can progress rapidly, leading to various complications such as septic shock, acute respiratory distress syndrome (ARDS) and even death^{2,3}. Previous systematic reviews reported that 19.2% to 21.33% of COVID-19 patients progressed to severe form^{4,5}.

Previous studies reported socio-demographic factors (older age, male sex)^{4,6,7}, co-morbidities (chronic pulmonary disease, chronic kidney

1. Besut District Health Office, Kampung Raja, Besut, Terengganu, Malaysia.
2. Setiu District Health Office, Bandar Permaisuri, Setiu, Terengganu, Malaysia.
3. Terengganu State Health Department, Kuala Terengganu, Terengganu, Malaysia.

Correspondence to: Dr Hafizuddin Awang. Public Health Medicine Specialist, Besut District Health Office, Kampung Raja, 22200 Besut, Terengganu. **E-mail:** drhafizuddin@moh.gov.my

disease, obesity, diabetes, hypertension, cardiovascular disease)^{4,6}, clinical symptoms (fever, cough, diarrhea, breathlessness)^{5,6}, and laboratory findings (increased C-reactive protein, decreased lymphocyte count, increased procalcitonin, increased D-Dimer)^{4,6,7}, were significantly associated with severe COVID-19 infection.

In Terengganu state of Malaysia, the number of COVID-19 cases fluctuated depending on the movement control order (MCO) implementation. Following the lift of inter-state travel ban in December 2020, Terengganu received a surge of COVID-19 cases in January 2021 and therefore, inter-state travel ban was re-implemented in Malaysia⁸. As strict MCO is no longer seen as a business-friendly measure in many countries including Malaysia⁹, the government of Malaysia gradually opened district borders in majority of states for economic recovery. The Ministry of Health Malaysia attempts to protect people from developing severe disease or dying from COVID-19 besides implementing containment strategy as well. To the best of our knowledge, there is no well-published study on risk factors for severe COVID-19 infection in the east coast region of peninsular Malaysia, and in Terengganu state of Malaysia particularly. We aimed to determine the predictive factors for severe COVID-19, particularly based on wide spectrum of clinical symptoms to facilitate public health and clinical physicians in anticipating severe stage of COVID-19 and hence, reduce the fatal complications and mortality rate among COVID-19 patients in Terengganu. The determination of predictive factors for severe COVID-19 infection would enable the identification of high-risk patients in Terengganu who may benefit from close monitoring, aggressive supportive care and early intervention.

Materials and Methods

A case-control study was conducted in Terengganu State Health Department which included all COVID-19 cases notified to Terengganu State Health Department from 1st March 2020 until 31st January 2021. Cases were severe COVID-19 patients (COVID-19 patients grouped in category IV or V upon diagnosis) while controls were mild COVID-19 patients (COVID-19 patients grouped in category I, II or III upon diagnosis)^{1,6}. The ratio of case to control was 1:5. The study samples were individuals with laboratory reverse transcription

polymerase chain reaction (RT-PCR) confirmed positive test for COVID-19. The sample size was calculated using two-proportion formula for each variable of associated factors for severe COVID-19 infection using Power and Sample size calculation software¹⁰. The minimal required sample size was 246 using the proportion of mild COVID-19 cases by the factor of male (0.4)⁷, an estimated proportion of 0.18, control to case ratio of 5, 5% type 1 error and 80% power. In the inferential part of the study, we employed simple random sampling for control group recruitment for mild COVID-19 patients from the total number of COVID-19 cases in Terengganu. For severe COVID-19 patients (case group), convenient sampling method was applied due to limited number of samples.

Data were collected from Terengganu state COVID-19 online registry and SIMKA Outbreak system (an online database for COVID-19 test results reporting) and recorded in patient's proforma. The retrieved information for independent variables included socio-demographic and clinical characteristics such as age, gender, presence of comorbidity, presence of symptoms like fever, cough, sore throat, coryza, myalgia, headache, anosmia, ageusia, diarrhoea and dyspnoea. The dependent variable was the severity of COVID-19 either mild or severe form, which was decided upon diagnosis of COVID-19. In this study, diagnosis of COVID-19 was made based on positive RT-PCR test result. Patients with either asthma, diabetes, hypertension, chronic kidney diseases, chronic pulmonary diseases, chronic cardiac diseases, or immunodeficiency state is classified as having comorbidity. We defined stages I to III COVID-19 as mild form, while stages IV to V as severe form of COVID-19^{1,6}.

Statistical analysis

Data entry and analysis were done using SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Descriptive statistics with mean and standard deviation (SD), frequency and percentages were calculated. Simple and multiple logistic analyses were employed to determine the predictive factors for severe COVID-19. A p -value < 0.25 from univariable analysis and clinically important variables were selected for multiple logistic regression analysis. In the final model, a p -value < 0.05 was considered statistically significant.

Results

From 1st March 2020 until 31st January 2021, a total of 2,142 positive cases in Terengganu were confirmed with RT-PCR testing and notified to Terengganu State Health Department. The proportion of patients diagnosed with severe COVID-19 was 2.1% (95%CI: 0.01, 0.03) or 44 patients. Severe COVID-19 patients in Terengganu had higher mean age as compared to mild COVID-19 patients, and majority of severe COVID-19 patients were male and had comorbidity (Table 1). Among severe COVID-19 patients, fever and cough were among the most common symptoms with 68.2% and 63.6%, respectively (Table 2). For inferential study, 220 patients were randomly selected among the 2,098 mild COVID-19 patients as a control group, thus making the ratio of severe COVID-19 subjects (44 patients in case group) to control subjects 1:5. Using multiple logistic regression analysis, older age, presence of comorbidity and having symptoms of fever, cough and anosmia were the significant predictive factors for severe COVID-19 in Terengganu (Table 3).

Table 1: Characteristics of COVID-19 patients in accordance to their severity in Terengganu state of Malaysia (n=2142)

Characteristics	Frequency (%)	
	Mild COVID-19 (n=2098)	Severe COVID-19 (n=44)
Age*	33.04 (±17.36)	57.57 (±16.49)
Gender		
Female	826 (39.4)	18 (40.9)
Male	1272 (60.6)	26 (59.1)
Comorbidity		
Absent	1918 (91.4)	19 (43.2)
Present	180 (8.6)	25 (56.8)

*Mean(±SD)

Table 2: Clinical symptoms among COVID-19 patients in accordance to their severity in Terengganu state of Malaysia (n=2142)

Clinical symptoms	Frequency (%)	
	Mild COVID-19 (n=2098)	Severe COVID-19 (n=44)
Fever		
No	1760 (83.9)	14 (31.8)
Yes	338 (16.1)	30 (68.2)

Cough		
No	1826 (87.0)	16 (36.4)
Yes	272 (13.0)	28 (63.6)
Sore throat		
No	1926 (91.8)	38 (86.4)
Yes	172 (8.2)	6 (13.6)
Coryza		
No	1978 (94.3)	34 (77.3)
Yes	120 (5.7)	10 (22.7)
Myalgia		
No	2071 (98.7)	43 (97.7)
Yes	27 (1.3)	1 (2.3)
Headache		
No	2053 (97.9)	41 (93.2)
Yes	45 (2.1)	3 (6.8)
Anosmia		
No	2015 (96.0)	39 (88.6)
Yes	83 (4.0)	5 (11.4)
Ageusia		
No	2053 (97.9)	44 (100.0)
Yes	45 (2.1)	0 (0.0)
Diarrhoea		
No	2084 (99.3)	43 (97.7)
Yes	14 (0.7)	1 (2.3)
Dyspnoea		
No	2082 (99.2)	38 (86.4)
Yes	16 (0.8)	6 (13.6)

Table 3: Factors associated with severe COVID-19 among patients in Terengganu state of Malaysia by simple and multiple logistic regression (n=264)

Characteristics	Crude OR (95% CI) ^a	p-value ^a	Adjusted OR (95% CI) ^b	p-value ^b
Age	1.07 (1.05, 1.09)	<0.001*	1.07 (1.03, 1.11)	<0.001*
Gender				
Female	1.00		-	
Male	1.00 (0.52, 1.93)	1.000	-	-
Comorbidity				
Absent	1.00		1.00	
Present	15.71 (7.23, 34.12)	<0.001*	5.97 (2.09, 17.01)	0.001*
Fever				
No	1.00		1.00	
Yes	8.57 (4.19, 17.53)	<0.001*	4.78 (1.63, 14.05)	0.004*
Cough				
No	1.00		1.00	

Characteristics	Crude OR (95% CI) ^a	p-value ^a	Adjusted OR (95% CI) ^b	p-value ^b
Yes	9.57 (4.68, 19.56)	<0.001*	4.81 (1.70, 13.60)	0.003*
Sore throat				
No	1.00		-	
Yes	1.13 (0.44, 2.92)	0.803	-	-
Coryza				
No	1.00		1.00	
Yes	3.75 (1.57, 8.95)	0.003*	1.13 (0.33, 3.88)	0.843
Myalgia				
No	1.00		-	
Yes	2.54 (0.23, 28.58)	0.452	-	-
Headache				
No	1.00		-	
Yes	1.94 (0.49, 7.62)	0.343	-	-
Anosmia				
No	1.00		1.00	
Yes	3.39 (1.06, 10.93)	0.040*	8.39 (1.39, 50.33)	0.020*
Ageusia				
No	1.00		-	
Yes	0.00 (0.00, 0.00)	0.999	-	-
Diarrhoea				
No	1.00		-	
Yes	2.54 (0.23, 28.58)	0.452	-	-
Dyspnoea				
No	1.00		-	
Yes	1.84 (0.42, 7.42)	0.441	-	-

*p-value < 0.05 ^aSimple logistic regression^bMultiple logistic regression

Forward LR method applied.

No multicollinearity and no interaction found.

HosmerLemeshow test, p-value= 0.873

Classification table 90.9% correctly classified.

Area under Receiver Operating Characteristics (ROC) curve was 94.2%.

Discussion

The proportion of severe COVID-19 infection in Terengganu state (2.1%) is relatively lower than the national proportion (8.0%) as reported in the previous Malaysian nationwide study⁶. Possible explanation to this lower proportion of severe COVID-19 infection could be attributed to precise and timely contact tracing and quarantine among potentially infected individuals in Terengganu as 91.2% of quarantined individuals in Terengganu turned out to be positive for COVID-19¹¹. Moreover, public health authorities (all district health offices) in Terengganu managed to provide early diagnosis and treatment to infected individuals in Terengganu as depicted by considerably low mean RT-PCR cycle threshold value (26.15) among COVID-19 cases in another study in Terengganu⁸. These timely and efficient public health interventions enabled us to provide early treatment and directly avert progression to severe form of COVID-19.

Our study reported cases with advanced age tend to acquire severe form of COVID-19 as similarly reported in previous Malaysian study⁶. Possible explanation for tendency of elderly to acquire severe COVID-19 is due to age-related immunocompromised state and concomitant infections which are commonly associated with elderly which subsequently posed higher risk for SARS-CoV-2 transmissibility¹².

Our finding highlighted the role of comorbidity in predisposing to severe COVID-19 which is congruent with previous literatures reporting pre-existing medical conditions such as chronic obstructive pulmonary disease, cerebrovascular diseases, cardiovascular diseases, hypertension, diabetes and obesity as strong predictors for severe COVID-19^{5,6}. As comorbidities are prevalent among elderly patients, the reason for COVID-19 disease progression is strongly attributed to age-related changes in the geriatric population such as weaker immune function, alterations in physiologic functions of the respiratory system

and also tendency of elderly towards dysfunction of multi-system organ and even failure¹³.

Among our COVID-19 cases, the most common presenting symptoms were fever and cough. Patients with these symptoms were more likely to progress to severe form of COVID-19 infection. Consistent high-grade fever in COVID-19 is regarded as a sign of severe infection. In a previous study, high grade fever ($>39^{\circ}\text{C}$) is significantly associated with the development of ARDS¹⁴. Fever in early stage of COVID-19 aims to boost immunity as our body's immune system responds to the viral replication. However, if the viral infection persists, it may cause dysregulation of inflammation which may cause cytokine storm and lead to unremitting fever. Subsequently, fever promotes further inflammation and severity of COVID-19¹⁵. Meanwhile, a study in China reported cough with chest pain and dyspnoea was significantly associated with COVID-19 severity. Chest pain may result from the pleural inflammation while dyspnoea is related to the severe damage to alveoli in severe COVID-19 patients¹⁶.

Individuals with anosmia had 8 times higher odds of getting severe form of COVID-19. COVID-19 patients tend to have anosmia as nasal epithelial cells demonstrate strong angiotensin converting enzyme 2 (ACE2) expression during SARS-CoV-2 infection, hence permitting extensive viral entry¹⁷. In experimental studies, olfactory neurons act as an entry site for neuro-invasion by SARS-CoV-2, which may be channelled to the central nervous system via a synapse-connected route. Subsequently, SARS-CoV-2 will induce direct neuronal injury within brainstem cardiorespiratory centres¹⁸. Therefore, we may postulate that the disease progression to severe form and respiratory failure in COVID-19 patients could be linked to the neuro-invasive capability of SARS-CoV-2.

This study had several limitations. Laboratory investigations were not included as part of the studied variables as these investigation results were not readily available in the COVID-19 online registry and SIMKA Outbreak system. Moreover,

our sample size for severe COVID-19 cases was relatively small. Therefore, longer study duration is needed to enable more cases recruitment. Apart from that, other possible factors such as health seeking behaviour of patients and accessibility to healthcare were not explored in this study, as these factors may contribute to the progression of severe COVID-19 infection as well.

Conclusion and recommendations

In conclusion, patients with advanced age, comorbidity, and presented with symptoms of fever, cough and anosmia were more likely to develop severe COVID-19 infection. Our results might be helpful in early prediction and risk reduction of mortality in patients with advanced age and comorbidity infected with COVID-19. The occurrence of the predictive symptoms (fever, cough, anosmia) could help clinicians identify the disease severity in clinical practice. Identifying predictive factors of severe COVID-19 will aid in assessment for early hospitalization and reduce mortality. Future studies with larger samples of the control group and inclusive of variables on laboratory parameters are recommended.

Conflict of interest: The authors declared that we have no conflict of interest in term of financial, institutional, and other possible relationships.

Ethical approval issue: This study received approval from the Medical Review and Ethical Committee (MREC) from National Institute of Health (NIH), Ministry of Health Malaysia NMRR-21-30-58174.

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