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Factors affecting the disease severity of COVID-19 patients in an emergency setting

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Coronavirus disease 2019 (COVID-19) is a highly contagious disease with a fast rate of spread. A present issue concerns a new variant of the virus with a more robust transmission ability and infection power than the original variant.
Objectives. The aim of this study was to analyse factors affecting the disease severity of COVID-19 patients in an emergency setting.
Material and methods. This study was conducted in UKRIDA Hospital. A total of 262 patients were included based on inclusion and exclusion criteria using non-probability consecutive sampling. The dependent variable was the severity of COVID-19 based on the New Early Warning Score 2 (NEWS2). The independent variables were age, gender, hypertension, diabetes mellitus, atherosclerosis, onset to admission interval, haemoglobin concentration, renal function and liver function. The data was collected from medical record and was analysed using the Chi-square or Mann-Whitney test and multinomial logistic regression.
Results. The results showed mild severity of COVID-19 (84.4%) followed by moderate (9.9%) and severe COVID-19 (5.7%). We also found that age ($p = 0.003$), hypertension ($p = 0.095$), diabetes mellitus ($p = 0.191$), atherosclerosis ($p = 0.004$), onset to admission interval ($p = 0.$), renal function ($p = 0.048$) and liver function ($p = 0.007$) were eligible for multivariate analysis. Further analysis showed that age ($p = 0.038$) and diabetes mellitus ($p = 0.034$) are the most significant factors related to the severity of the disease.
Conclusions. Age and diabetes mellitus are significant factors contributing to the severity of COVID-19 in an emergency setting.
Key words: COVID-19 pandemic, severity of illness, health correlates.

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Background

Coronavirus disease 2019 (COVID-19) is a new type of pneumonia that was first discovered in December 2019 [1]. This disease is highly contagious with a fast rate of spread [2]. Since it was first announced by the World Health Organization (WHO), more than 169 million people have been infected, with the death toll reaching more than 3.5 million. In Indonesia, the number of people infected with COVID-19 has reached 1.8 million, with the number of deaths amounting to more than 50 thousand people (approx. 18.4%) [3]. Indonesia is the fourth most populous country in the world with lower-middle income levels, which currently has the highest confirmed cases and deaths from COVID-19 in Southeast Asia, which also ranks second in Asia after India [4].

Currently, the world is still trying to control the spread of COVID-19 through lockdowns in several regions and mass vaccination programmes [5]. However, another problem has arisen with a new variant of the virus with a more robust transmission ability and infection power than the original variant [6, 7]. The emergence of new variants is caused by a mutation process, which has caused the second wave of infection that is happening at present [8]. A study in Ontario, Canada, found that new variants, or Variants of Concern (VOCs), accounted for 67% of all cases of SARS-CoV-2 infections in that country. Compared to the previous variant, VOCs were associated with an increased risk of hospitalisation of up to 63%, an increased risk of intensive care unit (ICU) admission up to 103% and an increased risk of death from COVID-19 by up to 56% [9]. Regarding the spread of VOCs infection, Indonesia experienced an increase in the number of cases per day by around 5,446 compared to the previous week of approximately 3,557 cases per day, based on surveillance data on 26 May 2021 [10]. In addition to the number of cases that are continue to increase, the incidence rate of mortality in Indonesia is still relatively high compared to the rest of the world and other countries in Asia [11]. Besides the significant increase in cases, the long-term impact of COVID-19 is also worrying. Previously, there was a misconception that all COVID-19 patients would recover in two weeks. However, there are symptoms that are long lasting, even if the patients experienced mild symptoms or was not admitted to hospital. This condition is called as long COVID [12].

Researchers continue to look for innovations in handling COVID-19, including how to predict the deterioration of COVID-19 and further possible events [13]. It was reported that the National Early Warning Score 2 (NEWS2) can be applied as a sensitive method for predicting the worsening condition of COVID-19 patients. NEWS2 shows superior accuracy compared to COVID-GRAM in estimating the likelihood of patients' conditions becoming critical [14]. Therefore, this study aims to determine factors affecting the disease severity of COVID-19 patients in emergency settings based on NEWS2.

Objectives

The aim of this study was to analyse factors affecting the disease severity of COVID-19 patients in an emergency setting.

Material and methods

Study design

This analytical study was conducted with a cross-sectional design.

Population and sample

The total population included confirmed COVID-19 patients who presented to the emergency room at UKRIDA Hospital (West Jakarta, DKI Jakarta) from January to May 2021. Non-probability consecutive sampling was used to collect the participants. A total of 262 patients were eligible and became the sample of this study. Total samples were measured using the slovin formula, with a 95% confident interval. Participants included in this study were confirmed COVID-19 patients aged more than 18 years who presented to the emergency room between January and May 2021. On the other hand, we excluded participants who were confirmed COVID-19 but had been fully or partially vaccinated, had congenital defects such as a heart congenital anomaly or had a history of being infected by COVID-19.

Study instrument

Data collection was carried out using secondary data collected from the Medical Record Installation of UKRIDA Hospital from January to May 2021. There were ten variables observed in this study, such as the severity of COVID-19 measured by the New Early Warning Score 2 (NEWS2), classified into mild: low (score 1–4), moderate: medium (score 5 and 6 or score of 3 in any individual parameter) and severe: high (score > 7); gender (male or female); age divided into 18–45 years and > 45 years; history of hypertension; history of diabetes mellitus; history of atherosclerosis, which is defined as patients who have experienced a heart attack or stroke confirmed by medical doctors; onset to admission (O–A) interval, which is calculated as time between the onset of the first symptoms (fever, cough, shortness of breath/dyspnoea, flu, diarrhoea, anosmia and ageusia) and patient admissions to the emergency ward, categorised by less than seven days and more than seven days; haemoglobin (Hb) level divided to anaemia, defined as Hb < 13 gr/dl for male or Hb < 12 gr/dl for female, and normal, defined as Hb ≥ 13 gr/dl for male or Hb ≥ 12 gr/dl for female; renal function tests divided to impaired, defined as elevation of creatinine level more than 1-fold baseline, and non-impaired, defined as normal to elevation 1-fold normal of creatinine level; and liver enzymes tests divided to impaired, defined as elevation of aspartate transaminase (AST) and/or alanine transaminase (ALT) level more than 1-fold baseline, and non-impaired, defined as normal to elevation 1-fold normal of AST and/or ALT level.

Data analysis

Data was analysed using SPSS software. Descriptive analysis was conducted to determine the characteristics of all participants included in the study. Following the prior analysis, a bivariate analysis with the Chi square or other alternatives was performed to analyse the relationship between each factor. Factors with a *p*-value < 0.25 were considered statistically significant and would be further analysed with multinomial logistic regression to determine the most dominant influence among all the deterioration risks of COVID-19.

Ethical approval

Approval for this study was obtained from the Medical and Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Krida Wacana Christian University, Indonesia (approval No: 1114/SLKE-IM/UKKW/FKIK/KE/VII/2021).

Results

Table 1. Subject characteristics

Characteristics	Category	Frequency	Percentage
Age	> 45 years 18–45 years	168 94	64.1% 35.9%
Gender	male female	132 130	50.4% 49.6%
COVID-19 severity	mild moderate severe	221 26 15	84.4% 9.9% 5.7%
Hypertension	yes no	90 172	34.4% 65.6%
Diabetes mellitus	yes no	37 225	14.1% 85.9%
Atherosclerosis	yes no	38 224	14.5% 85.5%
Onset to admission interval	> 7 days ≤ 7 days	39 223	14.9% 85.1%
Haemoglobin concentration	anaemia normal	53 209	20.2% 79.8%
Renal function	impaired non-impaired	7 255	2.7% 97.3%
Liver function	impaired non-impaired	27 235	10.3% 89.7%

Table 2. Independent factors analysed by bivariate analysis

Variable	Severity						*p*
	Mild		Moderate		Severe		
	n	%	*n*	%	*n*	%	
Age							
> 45 years	132	50.4%	23	8.8%	13	5.0%	**0.003***
18–45 years	89	34.0%	3	1.1%	2	35.9%	
Gender							
male	110	42.0%	14	5.3%	8	3.1%	0.900*
female	111	42.4%	12	4.6%	7	2.7%	
Hypertension							
yes	70	26.7%	12	4.6%	8	3.1%	**0.095***
no	151	57.6%	14	5.3%	7	2.7%	

Table 2. Independent factors analysed by bivariate analysis

Variable	Severity						*p*
	Mild		Moderate		Severe		
	n	%	*n*	%	*n*	%	
Diabetes mellitus							
yes	29	11.1%	2	0.8%	6	2.3%	**0.191**†
no	192	73.3%	24	9.2%	9	3.4%	
Atherosclerosis							
yes	26	9.9%	8	3.1%	4	1.5%	**0.004**†
no	195	74.4%	18	6.9%	11	4.2%	
Onset to admission interval							
> 7 days	28	10.7%	6	2.3%	5	1.9%	**0.016**†
≤ 7 days	193	73.7%	20	7.6%	10	3.8%	
Haemoglobin concentration							
anaemia	42	16.0%	8	3.1%	3	1.1%	0.369*
normal	179	68.3%	18	6.9%	12	4.6%	
Renal function							
impaired	4	1.5%	2	0.8%	1	0.4%	**0.048**†
non-impaired	217	82.8%	24	9.2%	14	5.3%	
Liver function							
impaired	18	6.9%	5	1.9%	4	1.5%	**0.007**†
non-impaired	203	77.5%	21	8.0%	11	4.2%	

* Chi-square test, † Mann-Whitney test.

Table 3. Variables affecting the disease severity of COVID-19 patients according to the results of multinomial logistic regression

Variable	Category	OR (95% CI)		*p*
		Mild to severe	Moderate to severe	
Age	> 45 years old (Ref)	1	1	**0.038**
	18–45 years old	2.79 (0.54–14.37)	0.69 (0.08–5.40)	
Hypertension	yes (Ref)	1	1	0.980
	No	0.92 (0.26–3.24)	0.86 (0.19–3.77)	
Diabetes mellitus	yes (Ref)	1	1	**0.034**
	No	2.76 (0.76–10.05)	10.62 (1.53–73.59)	
Atherosclerosis	yes (Ref)	1	1	0.124
	No	1.73 (0.43–6.89)	0.60 (0.12–3.01)	
Onset to admission interval	≥ 7 days (Ref)	1	1	0.349
	< 7 days	2.03 (0.57–7.24)	1.07 (0.22–5.08)	
Renal function	impaired (Ref)	1	1	0.580
	non-impaired	1.97 (0.18–20.77)	0.73 (0.05–9.97)	
Liver function	impaired (Ref)	1	1	0.174
	non-impaired	3.49 (0.89–13.65)	1.82 (0.34–9.59)	

Ref – reference category, CI – confident interval.

A total of 262 patients were included in the study (as shown in Table 1), with a majority of male participants (50.4%), age > 45 years (64.1%), followed by 18-45 years (35.9%). Patients with mild severity of COVID-19 (84.4%) were found most in this study, followed by moderate (9.9%) and severe COVID-19 (5.7%).

Table 2 shows that age ($p = 0.003$), hypertension ($p = 0.095$), diabetes mellitus ($p = 0.1$), atherosclerosis ($p = 0.004$), onset to admission interval ($p = 0.016$), renal function ($p = 0.048$) and liver function ($p = 0.007$) have a *p*-value less than 0.25 and were eligible to be included in multivariate analysis. Multivariate analysis in Table 3 showed that age ($p = 0.038$) and diabetes mellitus ($p = 0.034$) are the most significant factors related to the severity of the disease. Patients who are 18–45 years of age have 2.79 times increased risk of having mild COVID-19 than those who are over 45 years. We also found that patients without diabetes mellitus have 2.76 times increased risk of having mild COVID-19 and 10.62 times increased risk of having moderate COVID-19 than those who have diabetes mellitus.

Discussion

In this study, we found that age has a significant association with COVID-19 severity ($p = 0.038$). Several studies have also shown that age plays a significant role [15–18]. This condition was due to alterations in the quantity or quality of the immune system, which affects the response of immune cells and mediators in peripheral tissues. These changes determine not only the susceptibility to infection but also disease progression, clinical risk in the future and the response to vaccination [19]. The other factor leading to the elderly being more likely to have poor prognosis is that most of them have underlying conditions, like hypertension, diabetes, lung disease or heart disease [20]. Global statistical data indicates different case fatality rates among genders [21]. Men tended to develop more serious cases compared to women, according to the clinical classification of severity. The total number of deceased male patients is 2.4 times higher than that of females [22]. The ef-

fect of hypertension on critical COVID-19 patients was explored, and it was revealed that patients with hypertension were associated with a significantly increased risk of developing a critical illness (OR: 2.92; 95% CI: 2.26–3.77; and $p < 0.001$) [23]. Xiong et al. [24] also found that COVID-19 patients with hypertension had a greater chance of ICU admission ($p < 0.001$), mechanical ventilation ($p < 0.001$) and death ($p = 0.012$). We also found that people with diabetes mellitus were more likely to develop severe COVID-19 ($p = 0.34$). Guo et al. [25] reported that plasma glucose levels and diabetes are predicting factors for unfavourable clinical outcomes (morbidity and mortality) in COVID-19 patients ($p = 0.03$). The pathophysiology of COVID-19 and diabetes mellitus might be due to the reduced macrophage function. There are also other factors, such as chronic hyperglycaemia and inflammation, considered as possible reasons for an abnormal and ineffective immune response [26, 27]. Bouhanick et al. [28] also found that diabetes and age were associated with the occurrence of severe condition. A meta-analysis done by Palaiodimos et al. showed that the likelihood of death seems to be higher in diabetic patients hospitalised with COVID-19 compared to non-diabetic patients [29]. A meta-analysis done by de Almeida-Pititto et al. showed that diabetes, hypertension and especially cardiovascular disease are detrimental risk factors for severity and mortality in COVID-19 patients [30]. Atherosclerotic progression can lead to a severe inflammatory response and plays a role in the massive plasmatic concentration of cytokines [12]. COVID-19 patients with pre-existing cardiovascular issues have a higher risk of severe disease and death. In addition to that, the COVID 19 infection itself has been associated with multiple direct and indirect cardiovascular complications [32]. In a study by Alaa et al. [33] in England, the timing of hospital admission was associated with mortality in patients with COVID-19. The onset to admission interval ranged between 3 and 10.4 days, with the longest delay being in the 20–60 year age group [34]. Research carried out by Peng et al. showed that there was no association between the O-A interval and mortality or the length of hospital stay for severe-to-critical patients [35]. A cohort study in China show that in COVID-19 patients with anaemia, there is an elevation of C-reactive protein, procalcitonin and creatinine levels, which are related to severe COVID-19 [36]. Anaemia can be used as a factor that predicts poor prognosis in COVID-19 patients, including ventilator need and ICU admission or death [37]. However, several studies in Italy [38] and China [39] found no relationship between anaemia and severity of COVID-19. Several studies showed that poor renal function was related to poor COVID-19 outcome [40–42]. The association between renal function and COVID-19 can be addressed in two reciprocal ways: the effect of decreasing renal function with the severity of COVID-19, and the effect of COVID-19 with the renal function or renal disease. In this study, they mainly discussed the effect of decreasing e-GFR (decrease of renal function) with the severity of COVID-19 [40]. Krishnasamy et al. [43] showed that patients with liver enzyme elevations and the presence of a comorbidity were at higher risk of death (OR: 5.314; 95% CI: 2.278–12.393). Ahmed et al. [44] also found that the relation of AST, ALT and total bilirubin was related with the severity of COVID-19. Leulseged et al. [45] observed that there the increment of SGOT level (≥ 41 IU/L) was associated with a 1.358 times increased risk of having severe disease compared to those with normal SGOT level range ($p \leq 0.0001$).

Limitations of the study

We realise that as we were using secondary data from medical records, the collected data might be incomplete. Some of the data about the comorbid histories that were documented based on patient's information might be subjective. We also realise that there might be other factors that possibly related to the severity of COVID-19 but unfortunately those factors were not documented in the medical record.

Conclusions

We found that age and diabetes mellitus are significant factors contributing to the severity of COVID-19 in an emergency setting.

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