


The Relationship Between The Characteristics of COVID-19 Patients To Predict Mortality in The COVID-19 ICU Special Care

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ARTICLE INFO

Article history:

Received
15 December 2022

Accepted
30 December 2022

Manuscript ID:
JSOCMED-221217-3-8

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. dr. Aznan Lelo, PhD

Keywords

ABSTRACT

Introduction: The SARS-CoV-2 epidemic is sweeping the world with several waves of infections continuing. In some COVID-19 patients, this condition can develop into ARDS (acute respiratory distress syndrome) which requires ICU care with a mortality rate of 50-65 and the need for mechanical ventilation reaches 97%. The aim of this research was to know characteristics of COVID-19 patients to predict mortality in the Negative Pressure Isolation Room COVID 19 ICU at H. Adam Malik General Hospital

Method: Retrospective research method with secondary data sources of COVID-19 Negative Pressure Isolation Room ICU (RITN) patients at RSUP H. Adam Malik Medan for the period May 2021 – July 2021. The data collected was in the form of patient data including name, gender, age, medical record number, comorbidities, NLR, D-Dimer, Fibrinogen, PF ratio, use of oxygen supplementation, and length of ICU stay. Chi Square statistical analysis was used for categorical data, while the T-test or Mann Whitney was used for numerical data. Then between the variables an ANOVA test was carried out to assess the comparison of clinical characteristics with mortality.

Results: The results of this study indicate a higher mortality rate in women 41 people (57.7%), 56-65 years age group 26 people (36.6%), patients using ventilators 51 people (71.8%), comorbid hypertension 33 people (46.5%), Moderate PF Ratio were 44 people (62%) and Length of stay <10 days were 55 people (77.5%). The mean fibrinogen value in COVID-19 patients who died was 658.96 ± 674.98 , as well as the D-dimer value of 658.96 ± 674.98 and NLR of 11.06 ± 3.23 which showed a significant increase compared to patients Survivors of COVID-19 ($p < 0.05$).

Conclusion: A significant relationship was found between gender, age, breathing apparatus, D-dimer, Fibrinogen, NLR and length of stay with mortality of COVID-19 patients treated in the COVID Negative Pressure Room (RITN) ICU

Characteristics of Covid-19 Patients, severe degree of COVID-19, ICU, Negative Pressure Isolation Room, Mortality

How to cite: Taufik M, Wijaya DW, Lubis AP. The Relationship Between The Characteristics of Covid-19 Patients To Predict Mortality in The Covid-19 ICU Special Care. Journal of Society Medicine. 2022;1(3): 115-122

INTRODUCTION

The current SARS-CoV-2 epidemic is the third time a zoonotic coronavirus has infected humans over the past 18 years. As of March 24 2020, the number of confirmed cases and deaths of COVID-19 pneumonia in China was 81218 which shows that the death rate of COVID-19 is 4%. [1] As of January 2021, the number of people diagnosed with COVID-19 worldwide exceeded the number 86.7 million; while the case fatality rate in 222 countries and territories is 2.17%. The first case of COVID-19 was reported in Indonesia on March 2 2020 and as of January 8 2021, there were 818,386 confirmed cases and 23,947 deaths (CFR 2.92%). [2]

Some COVID-19 patients can develop ARDS (acute respiratory distress syndrome), heart failure and pulmonary embolism. ARDS is the most common etiology in COVID-19 patients to be admitted to the ICU. The average ICU admission occurs around 10 days after the onset of symptoms and 14 days after COVID-19 infection. The mortality rate for COVID-19 in the ICU is double that for other causes of viral pneumonia that require ICU.[3] The recorded prevalence of COVID ICU patients in China with ICU death within 28 days was 39% for (ICU population 344 patients), even reaching 97% in the subgroup of 100 patients requiring IMV.[4] Most patients admitted to the COVID ICU due to ARDS will eventually require prolonged mechanical ventilation (VM) and increase mortality. Reported mortality rates in ICU patients with severe COVID-19 range from 50-65%, and in patients requiring VM the rate is as high as 97%.[5]

In the results of laboratory tests, most of the patients experienced a decrease in the number of white blood cells, and lymphocytopenia. But in severe patients, the neutrophil count, D-dimer, blood urea, and creatinine levels were significantly higher, and the lymphocyte count continued to fall.[6] A report from Wuhan, China, showed that 71% of the 183 people who died from COVID-19 met the criteria for diffuse intravascular coagulation. Similar to other respiratory viral diseases, such as influenza, severe lymphopenia can occur in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. humoral and cellular immunity), impair lymphopoiesis and enhance lymphocyte apoptosis.[7]

In Patients. COVID-19 occurs a series of inflammatory processes in the body. Some evidence shows that the exacerbation of disease in COVID-19 is closely related to dysregulation and excessive cytokine release which is characterized by increased C-reactive protein (CRP), interleukin (IL) 6, and ferritin. Procalcitonin production is associated with the presence of bacterial endotoxins and inflammatory cytokines such as TNF, IL-1B and IL-6, so that procalcitonin can be used to predict respiratory tract infections with bacterial or viral etiology. Research on 1,735 research subjects with community acquired pneumonia (CAP) showed that the accuracy of procalcitonin in differentiating bacterial and viral infections reached 70%, with a sensitivity of 80.9% and a specificity of 51.6%.

METHOD

This research is analytic in nature with a retrospective research method with secondary data sources obtained from negative pressure ICU medical records. The research population is all patients treated for COVID ICU Negative Pressure (RITN) at RSUP HAM sourced from secondary medical record data. The number of samples obtained according to the calculation is 100 samples that have met the inclusion and exclusion criteria.

RESULTS

This research is analytic in nature with a retrospective research method with secondary data sources obtained from the Negative Pressure ICU (RITN) medical record data at RSUP HAM for the period March 2021 – July 2021. The research sample in this study was 100 samples.

Table 1 shows that there are 47 (47%) males, and 53 (53%) females. In the age distribution in the research range 18-35 years there were 15 people (15%), for the age range 36-45 years there were 17 people (17%), for the age range 46-55 years there were 31 people (31%), the age range 56-65 years as many as 37 people (37%). As for the outcome, 71 patients (71%) died, while 29 people left the Covid 19 ICU with negative results. The assistive devices used by the patients during their treatment were 19 people (19%) NRM, 26 people (26%) HFNC and 55 people (55%) using ventilators. In co-morbid patients, there were 25 people (25%) with DM, 25 people (25%) had DM co-morbidities, 10 people (10%) had asthma co-morbidities, 6 people (6%) had CKD co-morbidities, 4 people (4%) had comorbid COPD had 5 people (5%) comorbid pulmonary TB. For mild PF ratio, there were 14 people (14%), 63 patients with moderate PF, and 23 patients with severe PF (23%). The average NLR value in the study sample was 7.08 ± 3.32 , the average Fibrinogen value was 590.82 ± 439 and D. Dimer was 1509 ± 1305 .

Table 1. Sample Characteristics

Characteristics	n (%)
Gender n(%)	
Man	47 (47)
Woman	53 (53)
Age n(%)	
18 – 35 Years	15 (15)
36 – 45 Years	17 (17)
46 – 55 Years	31 (37)
56 – 65 Years	37 (37)
external	
DIE	71 (71)
Out of ICU Care	29 (29)
Device	
NRM	19 (19)
HFNC	26 (26)
VENTI	55 (55)
Comorbid	
There isn't any	13 (13)
DM	25 (25)
Hypertension	37 (37)
Asthma	10 (10)
CKD	6 (6)
COPD	4 (4)
Pulmonary TB	5 (5)
PF Ratio	
Mild > 200 mm Hg	14 (14)
Moderate 100 – 200 mm Hg	63 (63)
Weight < 100	23 (23)
NLR Mean ± SD	7.08 ± 3.32
Fibrinogen	590,82 ± 439
D Dimer	1509 ± 1305

Table 2. Covid-19 Mortality by Gender

Gender	Die	Get out of ICU	P
Male	30 (42.3)	17 (58.6)	0.02
Woman	41 (57.7)	12 (41.4)	

Table 2. shows an overview of Covid-19 mortality in terms of gender. As for the male sex, positive for Covid-19 experienced the death of 30 people (42.3%) out of 47 men and those who left the COVID-19 ICU with negative PCR results were 17 (58.6%). Meanwhile, 41 women (57.7%) died and 12 people left the COVID-19 ICU with negative PCR results. It was also explained in the table that the significant value of the relationship from mortality to sex was significant ($p < 0.05$).

Table 3. Covid-19 Mortality by Age Group

Age	Die	Get out of ICU	P
18 – 35 Years	10 (14.1)	17 (58.6)	0.01
36 - 45 Years	12 (16.9)	12 (41.4)	0.04
46 - 55 Years	23 (32.4)	8 (27.6)	0.02
56 - 65 Years	26 (36.6)	11 (37.9)	0.03

Table 3. shows an overview of Covid-19 mortality in terms of age. In the 18-35 year-old group who tested positive for Covid-19, 10 people (14.1%) died and 17 (58.6%) left the ICU COVID-19 with negative PCR results. Whereas in the age group 36-45 years who were positive for Covid-19, 12 people died (16.9%) and those who left the ICU COVID-19 with negative PCR results were 12 (41.4%), then the age group 46- 55

years who were positive for Covid-19 experienced the death of 23 people (32.4%) and those who came out of the COVID-19 ICU with negative PCR results were 8 (27.6%) and finally in the age group 56-65 years who were positive for Covid -19 died as many as 26 people (36.6%) and 11 (37.9%) left for outpatient treatment.

Table 4. Covid-19 Mortality of Respirators

Breathing apparatus	n (%)		P
	Die	Get out of ICU	
NRM	3 (4,2)	16 (55.2)	0.00
HFNC	17 (23.9)	9 (31)	0.04
VENTI	51 (71.8)	29 (100)	0.01

In Table 4, an overview of the Covid-19 Mortality is obtained for the breathing apparatus used. In the NRM use group who tested positive for Covid-19, 3 people (4.2%) died and 16 (58.6%) left for outpatient treatment. Whereas in the group using the HFNC who were positive for Covid-19, 17 people (23.9%) died and 9 (31.4%) left for outpatient treatment. 51 people died (71.8%) and 29 people left for outpatient treatment. It is also shown in the table that the significance value of the relationship between mortality and breathing apparatus is significant ($p < 0.05$).

Table 5. Covid-19 Mortality to Comorbids

Comorbid	n (%)		P
	Die	Get out of ICU	
There isn't any		13 (44.8)	0.001
DM	20 (28.2)	5 (17,2)	0.04
hypertension	33 (46.5)	4 (13,8)	0.000
Asthma	9 (12,7)	1(3,4)	0.001
CKD	4 (5,6)	2 (6,9)	0.00
COPD	2(2,8)	2 (6,9)	0.01
Pulmonary TB	3 (4.2%)	2 (6,9)	0.02

In Table 5, an overview of Covid-19 Mortality is obtained for the Comorbidities in the patient. In the patient group with co-morbid DM who was positive for Covid-19, 20 people (28.2%) died and 5 (17.2%) left for outpatient treatment. Whereas in the hypertension group positive for Covid-19, 33 people (46.5%) died and 4 (31.4%) left for outpatient treatment. 9 people (12.7%) and 1 (3.4) came out for outpatient treatment. Furthermore, in the group of patients who had CKD who were positive for Covid-19, 4 people (5.6%) died and 2 people who got out for outpatient treatment (6.9%).

Table 6. Covid-19 Mortality to PF Ratio

PF ratio	N(%)		P
	Die	Get out of ICU	
Mild > 200 mm Hg	5 (7)	9 (31)	
Moderate 100 – 200 mm Hg	44 (62)	19 (65.5)	0.04
Weight < 100	22 (31)	1 (3,4)	

Table 6. shows an overview of the Covid-19 mortality against the PF ratio used. In the Mild Ratio PF group who were positive for Covid-19, 5 people (7%) died and 9 (31%) left for outpatient treatment. Meanwhile, in the Moderate PF Ratio group, 44 people (62%) who were positive for Covid-19 died and 19 (56%) left for outpatient treatment. 22 people (31%) and 1 (3.4) came out for outpatient treatment. It is also

shown in the table that the significance value of the relationship between mortality and breathing apparatus is significant ($p < 0.05$).

Table 7. Covid-19 Mortality to Fibrinogen values

	Mean \pm SD		P
	Get out of ICU	Die	
Firbinogen	562.9 \pm 296.85	658.96 \pm 674.98	0.02

Table 7. shows an overview of Covid 19 mortality in terms of fibrinogen values. It was found that in patients who went home for outpatient treatment, the average Fibrinogen value was 562.9 ± 296.85 and in patients who died there was a Fibrinogen value of 658.96 ± 674.98 . The table shows that there is a significant relationship between the mortality of Covid 19 patients and the Fibrinogen value ($p < 0.05$).

Table 8. Covid-19 Mortality to the D Dimer value

	Mean \pm SD		P
	Die	Get out of ICU	
D Dimer	1665.73 \pm 1443.73	1128 \pm 732.52	0.02

Table 8. shows an overview of Covid 19 mortality against the D Dimer value. It was found that in patients who went home for outpatient treatment, the average D. Dimer value was 1128 ± 732.52 and in patients who died there was a D. Dimer value of 658.96 ± 674.98 . From the table it is shown that there is a significant relationship between the mortality of Covid 19 patients and the D. Dimer value ($p < 0.05$).

Table 9. Covid-19 mortality against NLR values

	Mean \pm SD		P
	Die	Get out of ICU	
NLR	11.06 \pm 3.23	7.13 \pm 3.61	0.02

Table 9. shows an overview of Covid 19 mortality in terms of NLR values. It was found that in patients who went home for outpatient treatment, the average NLR value was 7.13 ± 3.61 and in patients who died there was an NLR value of 11.06 ± 3.23 . The table shows that there is a significant relationship between the mortality of Covid 19 patients and the NLR value ($p < 0.05$).

Table 10. Covid-19 mortality on length of stay

Length of Treatment	n (%)		P
	Die	Get out of ICU	
< 10 Days	55 (77.5)	9 (31)	0.02
\geq 10 Days	16 (22.5)	20 (69)	

In Table 10, an overview of Covid-19 Mortality is obtained from the Length of Treatment. During the length of stay <10 days positive for Covid-19, 55 people (77.5%) died and 9 people (58.6%) got out of the ICU isolation of COVID-19. While on the length of treatment ≥ 10 16 people (22.5%) died and 20 people went home for outpatient treatment. It was also explained in the table that the significance value of the relationship from mortality to length of stay was significant ($p < 0.05$).

DISCUSSION

Various studies have reported high mortality among COVID-19 patients treated in the Intensive Care Unit (ICU). The ICU accepts critically ill patients and supports patients through critical phases. Approximately 10–15% of COVID-19 patients require hospitalization, and 20–30% of patients who are

hospitalized develop severe or life-threatening symptoms. Reported mortality rates for COVID-19 patients are 20–40% among hospitalized patients and 30–88% among critically ill patients admitted to the ICU, but these rates vary widely between countries and regions.[8-11]

The mortality rate of COVID-19 patients treated in the Negative Pressure ICU (RITN) at RSUP HAM in the 18-35 year age group was 10 patients (14.1%), the 36-45 year age group was 12 patients (16.9%) , the age group of 46-55 years were 23 patients (32.4%) and the age group 56-65 years were 26 patients (36.6%). A significant relationship was found between age and mortality of COVID-19 patients treated in the Negative Pressure ICU (RITN) at RSUP HAM ($p < 0.05$). 30 male COVID-19 patients who died (42.3%) while 41 female patients (57.7%) died and the results of the bivariate test found a significant relationship between gender and mortality of hospitalized COVID-19 patients. in the COVID Negative Pressure ICU (RITN) at RSUP HAM ($p < 0.05$).

Based on the type of oxygen supplement used, 3 patients (4.2%) died with use, 17 people (23.9%) in the HFNC group and 51 patients (71.8%) used mechanical ventilation. The results of the analysis showed a significant relationship between oxygen supplementation and mortality of COVID-19 patients treated in the Negative Pressure ICU (RITN) at RSUP HAM ($p < 0.05$). At the time of hospital admission, the Mean + (SD) BMI was in the obese range (ie, 30.8 [8.5]), and about a quarter of the patients were receiving supplemental oxygen.

In a 2020 cohort study conducted at 3 teaching hospitals in the United States. Of 217 critically ill patients, the mortality for patients requiring mechanical ventilation was 35.7% (59/165), with 4.8% of patients (8/165) still on a ventilator at the time of this report. Mortality was significantly associated with older age, lower body mass index, chronic kidney disease, higher Sequential Organ Failure Assessment score, lower PaO₂/Fio₂ ratio, higher d-dimer, higher C-reactive protein. higher, and acceptance of mechanical ventilation, vasopressors, renal replacement therapy, or vasodilator therapy. Nearly half of COVID-19 patients who received Invasive Mechanical Ventilation died based on reported CFR, but methods of reporting variable CFRs resulted in varying CFRs among studies. Reported CFRs were higher in older patients and in early pandemic epicenters, which may have been influenced by limited ICU resources. Preliminary reports on a cohort study from Seattle, where some of the first COVID-19 outbreaks occurred in the United States, indicated that 50–67% of patients admitted to the ICU and 71–75% of those who received invasive mechanical ventilation died.

Patients with comorbid DM who died were 20 people (28.2%), in the hypertension group there were 33 people (46.5%), in the asthma group there were 9 people (12.7%), in the CKD group there were 4 people (5.6%), in the COPD group there were 2 people (2.8%), in the pulmonary TB group there were 3 people (4.2%) The results of the analysis showed a significant relationship between comorbidity and mortality in COVID-19 patients treated in the ICU. Negative (RITN) COVID RSUP HAM ($p < 0.05$). Hypertension is the most common comorbidity and is found in more than half of patients, followed by diabetes in more than one third of patients. Pulmonary disease (including chronic obstructive pulmonary disease) occurs in up to one fifth of patients. Cancer was found in 2560 patients (12.3%), chronic kidney disease in 2628 patients (12.7%), and heart failure in 2343 patients (11.3%). Zha et al's study also showed that more than half of the patients ($n = 117$, 57.1%) had comorbid diseases. Compared with patients without comorbidities, patients with comorbidities had significantly higher mortality (HR: 1.83; 95% CI: 1.04–3.22), but significance disappeared after adjustment for multivariable factors (HR: 1.43 ; 95% CI: 0.76–2.69). The mortality rate for patients with comorbidities was 35.0%, and for patients with moderate and severe symptoms at diagnosis was 36.1%. 69). The mortality rate for patients with comorbidities was 35.0%, and for patients with moderate and severe symptoms at diagnosis was 36.1%. 69). The mortality rate for patients with comorbidities was 35.0%, and for patients with moderate and severe symptoms at diagnosis was 36.1%.

Patients with length of stay <10 days who died as many as 55 people (77.5%) while patients with length of stay ≥ 10 days who died as many as 16 people (22.5%) The results of the analysis showed a significant relationship between length of stay and mortality COVID-19 patients treated in the Negative Pressure ICU

(RITN) at RSUP HAM ($p < 0.05$). The mean length of stay in ICU was 20.6 days during Batch 1 (1 February–24 May 2020) and decreased to 16.3 days between periods and to 17.2 days during Batch 2 (5 October 2020–31 January 2021) and decreased more significantly to 16.0 days in Wave 3 (1 February 2021–30 June 2021). In the study by Dongelmans et al, the decreased length of stay in the ICU was caused by several reasons, namely a change in management for the most characteristic symptom of COVID-19 patients, namely hypoxia. In the process of several waves of COVID-19, there has been a decrease in the use of mechanical ventilation. On the other hand, because invasive mechanical ventilation has negative effects and can cause lung damage, COVID-19 patients are still given mechanical ventilation management as needed.[12]

The mean NLR value in patients who died was 7.06 ± 3.23 . From the results of the analysis, it was found that there was a significant relationship between the NLR value and the mortality of COVID-19 patients treated in the Negative Pressure ICU (RITN) at RSUP HAM ($p < 0.05$). The data of Cedano et al show that the majority of patients in the ICU with COVID 19 have decreased absolute lymphocyte counts. This finding is associated with poor outcomes in COVID 19 patients. According to some studies this pathogen can use ACE 2 receptors on lymphocytes to enter cells and cause direct viral toxicity. Another hypothesis suggests an indirect mechanism related to the release of proinflammatory cytokines in response to SARS-CoV2 infection which can activate the apoptotic pathway in lymphocytes.[12]The HR value of 1.053 found in the Al Mutair Study for neutrophil count implies that for each increase in neutrophil count, the estimated hazard (death) of COVID-19 patients in the ICU increases by 5.3%.[14]

The general mechanisms of increased D dimers are viremia and cytokine storm syndrome, in which increases in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF- α) are not controlled by increased anti-inflammatory factors. on the coagulation cascade. Hypoxia leads to hypoxia-induced activation of transcription factor-dependent signaling pathways, predisposing to thrombosis. This disease most often affects elderly patients and comorbidities. Advanced age and common comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease can increase the risk of thrombosis in patients.

CONCLUSION

A significant relationship was found between gender, age, breathing apparatus, D-dimer, Fibrinogen, NLR and length of stay with mortality of COVID-19 patients treated in the COVID Negative Pressure (RITN) ICU.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

This research has received no external funding.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

Not applicable.

REFERENCE

1. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020;55(5):2000524.
2. RI COVID-19 Task Force. Indonesia's COVID-19 distribution data. <https://covid19.go.id>. 2021.
3. Abkhoo A, Shaker E, Mehrabinejad MM, Azadbakht J, Sadighi N, Salahshour F. Factors Predicting Outcome in Intensive Care Unit-Admitted COVID-19 Patients: Using Clinical, Laboratory, and Radiologic Characteristics. Tran QK, editor. *Crit Care Res Practice*. 2021;2021:1–7.
4. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med*. 2020;180(10):1345.
5. Oliveira E, Parikh A, Lopez-Ruiz A, Carrilo M, Goldberg J, Cearras M, et al. ICU outcomes and survival in patients with severe COVID-19 in the largest health care system in central Florida. El-Tahan MR, editor. *PLoS One*. 2021;16(3):e0249038.
6. Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Sinto R, et al. Coronavirus Disease 2019 : Review of Current Literature Coronavirus Disease 2019 : Review of Current Literatures. *J Internal Medicine Indonesia*. 2020;7(1):45–67.
7. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020: 782–93.
8. Bass J, Singh A, Williams R, Lindner DH. Procalcitonin and COVID-19: a reliable clinical tool. *Res Sq*. 2020;1–7.
9. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. *Int J Antimicrobial Agents*. 2020;56(2):106051
10. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727–33.
11. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic targets. *Intensive Care Med*. 2020;46(4):586–90.
12. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Vol. 53, Cytokine and Growth Factor Reviews. *Elsevier Ltd*; 2020: 66–70.
13. Pitoyo CW, Tenda ED, Akhmad Z, Handoyo T, Ilyas M, Riyanto BS. Review article specifically for Covid-19 diagnostic and treatment compendium (interim) of the Indonesian Respiriology Association (Perpari). *J Internal Medicine Indonesia*. 2020;7(1):17–59.
14. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7(6):e438–40.