KnE Medicine

ICMEDH
The International Conference of Medicine and Health (ICMEDH)
Volume 2022

Knowledge E
enriching | engaging | empowering

Conference Paper

Risk Factors for Death in Covid-19 Patients at the Muhammadiyah University General Hospital of Malang

Gusti Galang Pambudi, Wildan Firmansyah, Harjuna Duta Nuswantara, Djoni Djunaedi

Muhammadiyah University General Hospital of Malang

ORCID
Gusti Galang Pambudi: https://orcid.org/0000-0002-7897-9146

Abstract.
The current global death rate of Covid-19 is 2.1%. In Indonesia, the rate is 3.3%. The Muhammadiyah University General Hospital of Malang is a Covid-19 referral hospital and in July 2021 there were 242 Covid-19 cases admitted to the wards with 48 deaths (19.8%). This study aimed to determine the risk factors of death in Covid-19 patients in terms of comorbidities. This was an analytical retrospective observational study, which used secondary data from July 2021. Several risk factors were examined, including gender, age (26 to 86 years), length of treatment (1 to 17 days), and comorbidities (diabetes mellitus, hypertension, heart failure, renal disorders, obesity, pregnancy, stroke, COPD, etc). We concluded that the most influential risk factors were male gender, age between 60 to 69 years, treatment duration of 1 to 5 days and diabetes mellitus.

Keywords: comorbidities, mortality, Covid-19, infection installation

Corresponding Author: Gusti Galang Pambudi; email: dalbolang@gmail.com

Published 15 September 2022

Publishing services provided by Knowledge E

Selection and Peer-review under the responsibility of the ICMEDH Conference Committee.

1. INTRODUCTION

Coronavirus Disease 19, or widely known as Covid-19 is a newly emerging respiratory disease caused by a new type of coronavirus called SARS-Cov-2, that can cause respiratory failure due to severe pneumonia [1]. In general, the symptoms of Covid-19 are high fever (temperature ≥ 38°C), cough, and difficulty in breathing. Other symptoms are complaints of shortness of breath that is getting heavy, fatigue, headaches, and digestive system disorders. In some patients, symptoms appear mild or even no symptoms. Patients positive for Covid-19 cases will be determined after undergoing various physical, laboratory, and radiological examinations. The most important laboratory tests are PCR (Polymerase Chain Reaction) and genome sequencing. Covid-19 transmission occurs through close contact of infected patients, splashes of infected patient's airway droplets, and virus-contaminated environment or objects. The dangerous complications

of Covid-19 are ARDS (acute respiratory disease syndrome), such as sepsis, sepsis shock, organ failure, and death [2].

By September 2021 a total of 224,180,441 confirmed cases have been reported globally with 4,621,205 death cases [3]. Covid-19 was predicted to have a mortality rate lower than SARS and MERS, in fact, its mortality rate is 2% - 2.3% or 20 times greater than common influenza. Covid-19 cases are more prevalent among older people having comorbidities such as cardiovascular disease, diabetes, hypertension, chronic respiratory disease, and cancer [4]. Data indicate Covid-19 is more prevalent among the elderly and those with comorbidities. The mortality rate is higher among older people [5].

Muhammadiyah University General Hospital of Malang (RSU UMM) has become a Covid-19 referral hospital since April 2020. The number of deaths from April 2020 to July 2021 is 251 (13.7%). The highest total death case in July 2021 was 81 cases (32%) and the death case on Covid-19 and Infection Installation was 48 cases (19,8%). This study aims to determine the risk factors for Covid-19 patients who died at RSU and examine them from several aspects, mainly of comorbid aspects.

2. METHODS

It is a retrospective study. The population involves all Covid-19 confirmed or probable patients who died at RSU UMM on July 2021. The laboratory-confirmed patients are defined as patients with a positive result on real-time reverse transcription-polymerase chain reaction (RT-PCR) for the presence of SARS-CoV-2 in either the nasal or pharyngeal swab specimens, irrespective of the clinical signs and symptoms. The probable patients are defined as patients with a positive result on Rapid Antigen Swab or patients with clinical signs, symptoms, and also laboratory-radiology findings lead to Covid-19. The research uses secondary data from medical record documents.

3. RESULT

There were a total of 276 Covid-19 cases treated at RSU UMM on July, 242 cases were admitted in our Covid-19 and Infection Installation. This was the highest number of cases that occurred during this pandemic. We also got the highest 81 cases (29.43%) and 48 admitted in our ward (19.38%).

We analyzed 48 cases of patients that died after the Covid-19 disease. We divided the data by gender, age, length of stay, use of a ventilator, cause of death, and comorbidities.

Of the decedents, 29 were male and 19 were female. The age ranges from 26-86 years old and the length of treatment time ranged from 1 to 17 days. Additional clinical information on the course of the disease was available in all cases. An overview of the clinical causes of death and documented comorbidities is given in Table 1.

The median age at death was 61 years (IQR: 49 to 70, range: 26 to 86 years). We divided them into 7 age groups ranging from less than 29 years old to over 80 years old, with the highest results in the 60 to 69 year age group. The length of treatment was divided into 3 categories, short (1-5 days), medium (6-10 days), and long (>10 days), the most in short treatment duration, which was 26 cases (54.2 %). There were 30 cases (62.5%) of death in our ward using no ventilator, and 18 cases (37.5%) were ventilator group. Chronic comorbidities and further relevant health conditions were analyzed. Only 4 cases had no comorbid. Diabetes Mellitus was the most prevalent chronic condition among decedents (43.8%), followed by hypertension (20.8%), heart failure (14.6%), chronic kidney disease (10.4%), obesity (8.3%), and the rest were other comorbid. Table 2 suggested severe chronic comorbidities and health conditions in the majority of the decadents.

4. DISCUSSION

As authors had already established, all SARS, MERS-CoV, and Covid-19 vary significantly in their severity. However, all three presented with the same spectrum of symptomatic changes that began with flu-like symptoms and escalate to ARDS in severe cases. The clinical manifestations in the case of Covid-19 showed a fairly consistent pattern without much variation over age and gender. The virus showed an incubation period of 3-7 days and may typically extend up to 14 days in some cases. However, there had been reported of the asymptomatic viral shedding for as long as 39 days in some rare cases [6].

The 48 cases of death showed that males dominate the group compared to females. Our findings concordance with other studies showing that the male sex is a strong predictor for higher risk of death in hospitalized adults with Covid-19, although it is not significant. In a meta-analysis of 3,111,714 reported global cases, male patients had a higher odd of death compared to female patients (Odds ratio = 1.4; 95% confidence interval = 1.31, 1.47). This raises the question of the importance of co-morbidities as drivers for mortality risk leading to the differences noted between sexes or differences in the immune system response between sexes. The association of higher odds of mortality in males with Covid-19 compared to female across age groups also raises

Table 1: Clinical Causes of Death and Documented Comorbidities in Hospitalized Patients with Covid-19.

Case	Age (years)	Gender	Length of treatment (days)	Use of Ventilator	Immediate causes of death	Condition leading to causes of death	Comorbidities and further relevant conditions
1	39	M	3	No	MODS	Pneumonia	Chronic Kidney Failure on Hemodialysis, Diabetes Mellitus, Anemia
2	77	F	1	No	MODS	Pneumonia	Diabetes Mellitus, Hypertension, Septicemia, Hypercoagulopathy
3	75	F	7	Yes	Respiratory Failure	ARDS	Diabetes Mellitus, Acute Kidney Injury, Sepsis, Hypercoagulopathy, Heart Failure
4	45	F	4	No	MODS	Pneumonia	Chronic Kidney Failure on Hemodialysis
5	85	M	5	Yes	Respiratory Failure	ARDS	Diabetes Mellitus, Hypertension, Heart Failure, Coronary Artery Disease
6	37	F	3	Yes	Respiratory Failure	ARDS	Anemia
7	63	F	2	Yes	Hypoxia	ARDS	Diabetes Mellitus, Electrolyte imbalance, Acute Kidney Injury, Septic Shock
8	35	F	16	No	Hypoxia	Pneumonia	Hypercoagulopathy, Trombositopenia
9	44	M	6	Yes	Respiratory Failure	ARDS	Diabetes Mellitus, Septic Shock, Bradycardia
10	67	M	3	Yes	MODS	Pneumonia	Hypertension Heart Disease, Hypertension, Diabetes Mellitus, Stroke, Encephalopathy, Electrolyte imbalance, Septic Shock
11	26	F	6	Yes	MODS	Pregnancy, ARDS	Pregnancy, Asthma, Obesity
12	77	F	8	Yes	Respiratory Failure	ARDS	Diabetes Mellitus, Acute Kidney Injury, Hypercoagulopathy, Obesity, Benign Paroxysmal Positional Vertigo, Hypoxic Ischemia Encephalopathy
13	49	M	2	No	Hypoxia	Pneumonia	-
14	51	M	10	Yes	MODS	Pneumonia	Diabetes Mellitus, Hypercoagulopathy, Septic Shock
15	82	M	5	No	Hypoxia	Pneumonia	Spondylosis Lumbar, Chronic Gastritis

Table 1: (Continued).

16	61	F	9	Yes	MODS	Pneumonia	Diabetes Mellitus, Hypoalbuminemia, Septic Shock
17	29	F	7	Yes	Respiratory Failure	Pregnancy, ARDS	Pregnancy, Hypoalbuminemia, Hypercoagulopathy
18	58	M	14	Yes	Respiratory Failure	ARDS	Sepsis
19	53	M	8	No	Hypoxia	Pneumonia	Chronic obstructive pulmonary disease, Diabetes Mellitus, Hypoalbuminemia
20	68	M	4	Yes	Respiratory Failure	ARDS	Hypercoagulopathy, Heart Failure
21	57	M	4	No	MODS	Pneumonia	Chronic Kidney Failure on Hemodialysis, Anemia
22	76	M	1	No	MODS	Pneumonia	Diabetes Mellitus, Hypoalbuminemia, Hypercoagulopathy
23	52	F	4	No	Hypoxia	Pneumonia	Diabetes Mellitus, Obesity, Hypertension
24	63	M	11	No	Hypoxia	Pneumonia	Hypercoagulopathy
25	56	M	3	No	MODS	Pneumonia	History of anxiety, Coronary Artery Disease
26	65	M	12	No	Hypoxia	Pneumonia	Hypercoagulopathy
27	46	M	6	No	Hypoxia	Pneumonia	Chronic Gastritis
28	49	M	12	No	Hypoxia	Pneumonia	Diabetes Mellitus, Hypoalbuminemia, Hypercoagulopathy
29	39	M	9	Yes	Respiratory Failure	ARSD	Congestive Heart Failure, Hypertension, Sepsis
30	65	F	1	No	MODS	Pneumonia	Coronary Artery Disease, Acute Decompensated Heart Failure
31	69	M	17	No	MODS	Pneumonia	Diabetes Mellitus, Hipoalbuminemia, Sepsis, Hypertension Heart Disease
32	86	F	4	No	MODS	Pneumonia	Sepsis
33	42	M	14	No	MODS	Pneumonia	Hypertension Heart Disease, Sepsis
34	73	F	1	No	Hypoxia	Pneumonia	-
35	69	F	5	No	MODS	Pneumonia	Anemia, Hypertension Heart Disease, Chronic Kidney Disease, Septic Shock

the question of the role of sex hormones in immune response, and the effect that age

Table 1: (Continued).

36	57	M	4	No	Hypoxia	Pneumonia	-
37	76	M	0	Yes	Respiratory Failure	ARSD	Atrial Fibrillation, Congestive Heart Failure, Anemia, Hypoalbuminemia
38	62	F	8	No	Hypoxia	Pneumonia	Hypertension
39	61	M	3	No	Hypoxia	Pneumonia	Diabetes Mellitus, Bisitopenia
40	67	F	2	No	Hypoxia	Pneumonia	Congestive Heart Failure, Diabetes Mellitus, Hypoalbuminemia
41	40	M	10	No	MODS	Pneumonia	Chronic Kidney Disease, Compartment Syndrome, Abscess at Regio Manus Sinistra, Stroke, Encephalopathy
42	77	F	4	No	Respiratory Failure	ARSD	Diabetes Mellitus
43	63	M	12	No	Hypoxia	Pneumonia	Dermatitis
44	58	F	13	Yes	Respiratory Failure	ARSD	Diabetes Mellitus, Hypoalbuminemia, Obesity, Hypoglycemia
45	55	M	14	Yes	Respiratory Failure	ARSD	Diabetes Mellitus, Hepatitis, Hypercoagulopathy, Hypertension Heart Disease, Sepsis
46	74	M	4	No	Hypoxia	Pneumonia	-
47	53	M	1	No	Hypoxia	Pneumonia	-
48	73	M	4	Yes	Respiratory Failure	ARSD	Diabetes Mellitus

had on sex hormone concentration [7]. Further studies were needed to determine the underlying mechanisms for this differential risk of death between male vs female.

There is a correlation between age and natural immunity as reviewed elsewhere and concluded that older people are particularly susceptible to developing more infections due to natural immunity decreases gradually in older age. Older people are also prone to adverse drug reactions which may be partly due to the reduced organ function at an older age or taking multiple medications because of comorbidities. The results of the current study show that people 50 years of age or older are at a significantly higher risk of death than those under the 50s. Linear regression with ACE2 gene expression in the nasal epithelium as dependent variable and age group as an independent variable, a recent study showed that compared with younger children, expression of the ACE2 gene significantly higher in older children ($p = 0.01$), young adults ($p < 0.001$), and adults ($p = 0.001$) who may partly explain why mortality was significantly higher in older patients, as identified in this study. Based on this evidence and from the findings current study,

Table 2: Summary of Death Data in the Covid-19 and Infection Installation RSU UMM.

Category	Total N =48
Median Age (IQR), years	61 (49-70)
Age group	
<29	2 (4.2%)
30-39	4 (8.3%)
40-49	7 (14.6%)
50-59	10 (20.8%)
60-69	13 (27.1%)
70-79	9 (18.8%)
>80	3 (6.2%)
Sex	
Male	29 (60,4%)
Female	19 (39.6%)
Length of treatment, days	
1-5	26 (54,2%)
6-10	13 (27%)
>10	9 (18.8%)
Use of Ventilator	
Yes	18 (37.5%)
No	30 (62.5%)
Immediate causes of death	
Respiratory Failure	14 (29.2%)
MODS	16 (33.3%)
Hypoxia	18 (37.50%)
Type of Comorbidity	
None	4 (8.3%)
Diabetes Mellitus	21 (43.8%)
Cardiovascular System	
Hypertension/ Hypertension Heart Disease	10 (20.8%)
Heart Failure	7 (14.6%)
Coronary Artery Disease	3 (6.3%)
Atrial Fibrillation	1 (2.1%)
Renal Disorders	
Acute Kidney Disease	3 (6.3%)
Chronic Kidney Disease	5 (10.4%)
Obesity	4 (8.3%)
Stroke	2 (4.2%)
Pregnancy	2 (4.2%)
Respiratory System	
Asthma	1 (2.1%)
COPD	1 (2.1%)
Other Condition	
Septicemia, Sepsis, Shock Sepsis	13 (27.1%)
Hypoalbuminemia	8 (16.7%)
Anemia	5 (10.4%)
Encephalopathy	3 (6.3%)
Electrolyte imbalance	2 (4.2%)
Chronic Gastritis	2 (4.2%)
Compartment Syndrome	1 (2.1%)
Dermatitis	1 (2.1%)
Abscess	1 (2.1%)
Bisitopenia	1 (2.1%)
Spondylosis	1 (2.1%)
BPPV	1 (2.1%)
History of anxiety	1 (2.1%)

it had postulated that patients over 50 years old might have higher ACE2 expression encoded by the ACE2 gene as well as having other conventional factors, for example, reduced immunity, low organ function, or comorbid that may be responsible for greater the risk of death [8].

The fatality of cases with Covid-19 was heavily dependent upon underlying health conditions and the most common comorbidities include Hypertension, Diabetes, Cardiac Conditions and Immunocompromised status. However, none of these conditions reflect absolute mortality, several patients with these health conditions had successfully recovered as survival groups [6].

In terms of comorbidities, Hypertension takes the main part, with patients being most likely to get Covid-19. However, patients with diabetes are the most at risk for the severe condition and poor prognosis. Another remarkable pattern emerging from recent studies is that the severity of pre-existing Cardiovascular conditions was inversely proportional before admission to death. However, the proportion of patients that progress to death has significantly less in cases with Cardiovascular in comparison to other comorbidities mentioned [9].

The cause of death of Covid-19 patients is not only due to damage to the lungs, but also the emergence of fibrotic tissue in other organs, such as the heart, brain, and peripheral nerves. Details are listed in Figures 1 and 2.

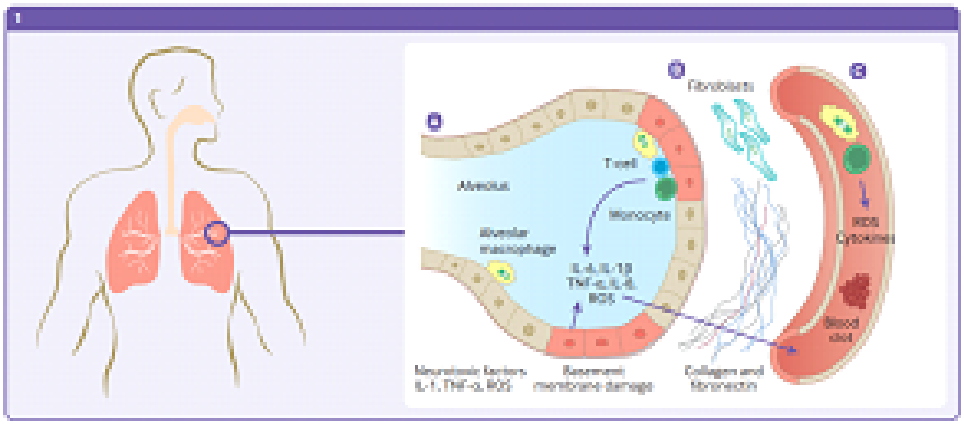

Figure 1: [10] In the alveoli of the lungs: (A) Chronic inflammation results in the sustained production of pro-inflammatory cytokines and reactive oxygen species (ROS) which are released into the surrounding tissue and bloodstream. (B) Endothelial damage triggers the activation of fibroblasts, which deposit collagen and fibronectin resulting in fibrotic changes. (C) Endothelial injury, complement activation, platelet activation, and platelet-leukocyte interactions, release of pro-inflammatory cytokines, disruption of normal coagulant pathways, and hypoxia may result in the development of a prolonged hyperinflammatory and hypercoagulable state, increasing the risk of thrombosis.

Several authors find that hypertension was the most common comorbid in Covid-19 patients. While in our hospital, diabetes mellitus to be the most frequent comorbid, followed by hypertension the β-cell pancreas produces insulin, blood sugar-lowering

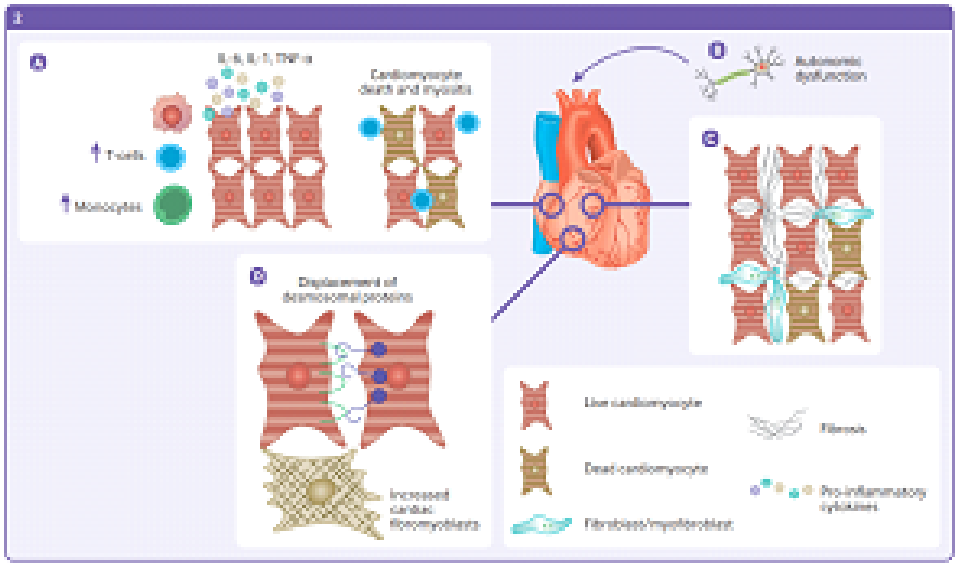

Figure 2: [10] In the heart: (A) chronic inflammation of cardiomyocytes can result in myositis and cause cardiomyocytes death. (B) Dysfunction of the afferent autonomic nervous system can cause complications such as postural orthostatic tachycardia syndrome. (C) Prolonged inflammation and cellular damage prompts fibroblasts to secrete extracellular matrix molecules and collagen, resulting in fibrosis. (D) Fibrotic changes are accompanied by an increase in cardiac fibromyoblasts, while damage to desmosomal proteins results in reduced cell-to-cell adhesion.

hormone, the α-cell pancreas produces glucagon, a blood sugar-increasing hormone. From the various study, Covid-19 destroy β-cell resulted in hyperglycemia. Viruses can also induce the production of several proteins, which can trigger an immune response that can also kill specific cells and alter insulin secretion. In obese people, insulin resistance may be an important aspect of the incidence of Covid-19. ACE2 is a potential link between insulin resistance and Covid-19 because the virus enters the host body via ACE2. ACE2 assists in the maintenance of the RAAS and similar abnormalities lead to insulin resistance and cardiovascular dysfunction. The degradation of angiotensin 2 results in a reduction in insulin resistance by reducing oxidative stress, increasing insulin signaling and insulin transport. Normalizing blood glucose and insulin levels were the most important, thereby reducing ACE2 expression and ultimately the severity of Covid-19 [11].

Angiotensin-converting enzyme 2 (ACE2), a membrane glycoprotein, is expressed the most in epithelial cells of the lungs, intestines, kidneys, and blood vessels. ACE2 played an important role in the breakdown of angiotensin-II and to some extent, angiotensin-I into peptides, angiotensin (1-7) and angiotensin (1-9), separately. ACE2/Angiotensin (1-7) had a significant anti-oxidant, anti-inflammatory, role in the protection of the lungs against acute respiratory distress syndrome as well as in the case of bird flu infection. The level of ACE2 expression was found to be reduced in cases of DM probably due

to glycosylation. That is why severe lung injury followed by acute respiratory distress syndrome (ARDS) with Covid-19 increases [11].

A previous diagnosis of HT increased the risk of all-cause death in Covid-19 patients who required hospitalization should of approximately 20% and independently of age and other cardiovascular comorbidities, such as atrial fibrillation and HF. In line with the vast majority of studies, our results support the observation that Covid-19 patients are generally older and more fragile than the general population. However, the specific association between HT and Covid-19 remains debatable and controversial. Some studies have linked the presence of HT to worse outcomes in Covid-19, whereas others consider HT to simply be a potential confounding factor for the real, causal relationship between gender, age, cardiovascular disease, increasing the mortality due to Covid-19 [12].

Mortality increased in patients prevented from continuing their previous treatment with ACEIs/ARBs during their hospital stay. Careful evaluation of medications used in hypertensive patients diagnosed with Covid-19 is mandatory. Very important to emphasize the scope of our study on HT treatment before hospital admission. In line with the evidence published to date, does not examine in-hospital management of Covid-19 patients as the main objective. Although the underlying mechanisms might be equally related to the ACE2/angiotensin 1-7/mas receptor axis, other studies are necessary to evaluate confounding factors, especially the incidence of cardiovascular complications and in-hospital treatment with ACEIs/ARBs that may alter the extent of the association of HT and its previous treatment with all-cause mortality [12].

5. CONCLUSION

While consistent with previous research showing that male gender, advanced age, and certain comorbidities, especially diabetes and hypertension are risk factors for Covid-19 death. While consistent with previous research showing that male gender, advanced age, and certain comorbidities, especially diabetes and hypertension are risk factors for Covid-19 death.

References

[1] Rozaliyani A, Savitri AI, Setianingrum F, Shelly TN, Ratnasari V, Kuswindarti R, et al. Factors associated with death in COVID-19 patients in Jakarta, Indonesia: An epidemiological study. Acta Med Indones. 2020 Jul;52(3):246–54.

[2] Israfil I, Wiliyanarti PF, Selasa P. Literature review: Risk of death in Covid-19 patients. Unnes Journal of Public Health. 2020;9(2):141–7.

[3] World Health Organization. Weekly epidemiological update on COVID-19 - 25 May 2021.

[4] The Health Ministry of Indonesia. The decree of health ministry No HK.01.07/Menkes/413/2020 about guidnce for prevention of Coronavirus disease 2019 (Covid-19). 2020.

[5] Sulistyowati ES, Muninggar SS, Silalahi V. Risk factors of Covid-19 confirmed died patients in Dr. Kariadi Hospital: A retrospective study. Indonesian Journal of Tropical and Infectious Disease. 2021;9(1):1.

[6] Garima S, Singh N. Fatality in COVID 19: An overview of causes of death and organ involvement. International Journal of Advances in Medicine. 2020;7(7):1190.

[7] Nguyen NT, Chinn J, De Ferrante M, Kirby KA, Hohmann SF, Amin A. Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. PLoS One. 2021 Jul;16(7):0254066.

[8] Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of sex, age, and comorbidities with mortality in COVID-19 Patients: A systematic review and meta-analysis. Intervirology. 2020 Dec;64(1):1–12.

[9] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020 May;323(18):1775–6.

[10] Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ. 2021 Jul;374:1648.

[11] Santoso A, Ph D, Pranata R, Wibowo A, Ph D. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information. Am J Emerg Med. 2020:1–6.

[12] Rodilla E, Saura A, Jiménez I, Mendizábal A, Pineda-Cantero A, Lorenzo-Hernández E, et al. Association of hypertension with all-cause mortality among hospitalized patients with COVID-19. J Clin Med. 2020 Sep;9(10):1–12.