



# Comparison of Length of Stay of Severe and Critical COVID-19 Patients with Diabetes Mellitus, Hypertension, and Other Comorbidities

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## Abstract

**Background:** Coronavirus Disease-19 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2). In 2020, a disease known as COVID-19 became a global pandemic. This disease can spread through the air or mucosal contact with the body. The impact of COVID-19 varies greatly from person to person and depends on various factors, including any pre-existing health conditions. This study aimed to determine the hospitalization period for severe and critical COVID-19 patients with comorbidities such as diabetes mellitus, hypertension, obesity, heart failure, stroke, pregnancy, coronary artery disease, and asthma in the Intensive Care Unit at RSUD Dr. Saiful Anwar in Malang.

**Methods:** This study used an observational analysis method by taking secondary data from medical records and out-of-hospital data of patients admitted to the Intensive Care Unit. The data that has been collected is carried out by a normality test using the Saphiro-Wilk test then the Kruskal-Wallis test and the Dunn test as a follow-up test.

**Results:** The study was dominated by subjects less than 60 years of age, male, and most had comorbidities. It was found that only in death outcome group has a significance value of  $P < 0.05$ , with the longest hospital stays in patients without comorbidities and patients with diabetes mellitus only (ICU Median=7.5 days), while the shortest length of stay was obtained in patients with comorbidities other than diabetes and hypertension (ICU Median=3.5 days).

**Conclusion:** The presence of multiple comorbidities in patients is associated with greater severity of illness, resulting in longer hospital stays among those who are discharged. Conversely, patients who experience death outcomes tend to have shorter lengths of stay in the hospital.

**Keywords:** comorbidities, COVID-19, diabetes mellitus, hypertension, length of stay

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## INTRODUCTION

Coronavirus Disease-19 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) virus. As of December 23, 2022, the World Health Organization (WHO) has reported a total of 651,918,402 confirmed COVID-19 cases worldwide.<sup>1</sup> While in Indonesia, as of December 23, 2022, there are 6,713,879 confirmed cases of COVID-19.<sup>2</sup> The spread of this disease can occur through the air or contact with body mucosae, such as eyes, nose, and mouth with body surfaces or objects containing the virus. The disease's incubation period is quite diverse, ranging from 2 to 14 days.

Common symptoms of COVID-19 are coughing, sore throat, shortness of breath, fatigue, and dizziness.<sup>3</sup>

The impact of the disease is quite diverse on each individual. Individuals who are of advanced age or have underlying health conditions are at a higher risk of experiencing severe symptoms from COVID-19.<sup>3</sup> About 15% of patients treated will experience severe conditions, and approximately 5% of them will fall into critical condition and require treatment in the intensive care unit and use a breathing apparatus in the form of a ventilator.<sup>4</sup>

Hypertension and diabetes mellitus are diseases often found in Indonesian society, and these two diseases are commonly found in individuals infected with COVID-19 as comorbidities. Research

suggests that people who have hypertension are at a greater risk of developing respiratory infections. This strongly indicates that patients fall to severe degrees if an individual with hypertension is infected with COVID-19. Having hypertension raises the chances of mortality and being admitted to an Intensive Care Unit (ICU).<sup>5</sup>

Individuals who suffer from diabetes mellitus are prone to facing severe complications and risks associated with COVID-19, which can lead to fatal outcomes. Such people are more susceptible to contracting the virus and developing medical challenges related to it.<sup>5</sup> In Indonesia, 49.9% of COVID-19-positive patients have hypertension, and 37% have diabetes mellitus.<sup>2</sup>

According to a research study conducted in London, COVID-19 patients worldwide have an average hospitalization period of 5 to 29 days, while their stay in the ICU ranges from 5 to 19 days.<sup>6</sup> Another study conducted in France found that COVID-19 patients with comorbid diabetes mellitus had a longer average hospital stay than those without this condition.<sup>7</sup> Furthermore, for patients with comorbid hypertension, 59% had a hospital stay of less than 9 days, while 41% had a hospital stay of 9 days or more.<sup>8</sup>

Regarding our knowledge, there is no available published data on the length of hospitalization of severe and critical COVID-19 patients with diabetes mellitus and hypertension in the ICU at Dr. Saiful Anwar Hospital, Malang. Therefore, the writer needs to conduct research related to "how to describe the length of hospitalization of severe and critical COVID-19 patients with comorbid diabetes mellitus and/or hypertension and/or other comorbidities at Dr. Saiful Anwar Hospital, Malang".

## METHODS

This study used an observational analysis method with a retrospective design regarding the length of hospitalization of severe to critical COVID-19 patients with comorbidities at Dr. Saiful Anwar Hospital, Malang, from August 2020 to 2021. The sample data is secondary data taken from the

medical records of COVID-19 patients in the ICU at Dr. Saiful Anwar Hospital, Malang.

The population of this study is medical records and hospital discharge data of patients who have been confirmed to have COVID-19 with severe to critical degrees. The data is collected from Dr. Saiful Anwar Hospital in Malang. The study only includes patients who meet specific inclusion criteria, which are as follows:

1. COVID-19 patients who have been confirmed through the Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) method with severe and critical criteria
2. Patients who have comorbid hypertension and/or diabetes mellitus and/or other comorbidities such as obesity, heart failure, stroke, pregnancy, coronary artery disease, asthma, that the results of examinations or laboratory results can prove.
3. COVID-19 patients treated in the ICU at Dr. Saiful Anwar Hospital who have severe to critical degrees with medical record data and hospital discharge data.

All existing data will be recorded and grouped according to predetermined criteria. The obtained data is then processed using a computer program, SPSS software version 25.

Furthermore, the Kruskal-Wallis test was used to compare the length of hospitalization in the Intensive Care Unit between the seven comorbid categories and continued with the Dunn test as multiple comparisons if significant results were obtained.

## RESULTS

This study took secondary data from the Medical Records of Saiful Anwar Malang Hospital, with a total sample of 378 medical records. Severe and critical COVID-19 patients in the ICU at Saiful Anwar Hospital were dominated by patients less than 60 years of age (63.2%), men (56.1%), and most of them had comorbidities (80.4%). The median length of hospital stays in the Intensive Care unit is 5 days, while the median length is 7 days. Detailed patient demographic data can be seen in Table 1.

Table 1. Demographic Data

Variables	n	%
Age Group		
<60 years	239	63.2
≥60 years	139	36.8
Gender		
Man	212	56.1
Woman	166	43.9
Comorbid		
Yes	304	80.4
No	74	19.6
Comorbid Categories		
No Comorbid	74	19.6
Diabetes Mellitus Only	37	9.8
Hypertension Only	39	10.3
Diabetes Mellitus and Hypertension	27	7.1
Diabetes Mellitus and Hypertension + Other Comorbidities	31	8.2
Diabetes Mellitus or Hypertension + Other Comorbidities	78	20.6
Other Comorbid	92	24.3
Length of Stay in Intensive Care Room		
<5 days	163	43.0
≥5 days	215	57.0
Length of Hospital Stay		
<7 days	178	46.5
≥7 days	202	53.5
Outcome		
Hospital discharge	105	27.8
Death	273	72.2

Patients usually spend an average of 5 days in the Intensive Care Unit during their hospital stay, with a range from 0 to 29 days. The most common length of stay is 3 days. Interestingly, patients without any comorbidities tend to have the longest ICU stays, averaging 8 days. In comparison, patients with diabetes mellitus or hypertension plus other comorbidities have shorter stays, with a median of 4 days. Among those with death outcomes, patients without any comorbidities and those with only diabetes mellitus had the longest ICU stays, averaging 7.5 days. Conversely, patients with other comorbidities (excluding diabetes and hypertension) had the shortest ICU stays, averaging 3.5 days (Table 2).

The median length of hospital stay is 7 days, with a range from 0 to 39 days, and the most frequently observed duration is 3 days. Patients with the longest hospital stays were those with only diabetes mellitus and patients with other comorbidities (excluding diabetes and hypertension), averaging 15 days. In contrast, patients with diabetes mellitus or hypertension plus other comorbidities had shorter stays, with a median of 12 days.

Table 2. Length of Stay of ICU Patients by Outcome in Each Comorbid Category

Comorbid Categories	Length of ICU Stay (Days)					
	Total		Hospital discharge		Death	
	N	Median	N	Median	N	Median
No Comorbid	74	7.50	22	8.00	52	7.50
Diabetes Mellitus only	37	7.00	5	6.00	32	7.50
Hypertension only	39	6.00	16	6.50	23	6.00
Diabetes Mellitus and Hypertension	27	6.00	6	6.50	21	4.00
Diabetes Mellitus and Hypertension plus Other Comorbidities	31	5.00	8	6.50	23	5.00
Diabetes Mellitus or Hypertension plus Other Comorbidities	78	5.00	20	4.00	58	5.00
Diabetes Mellitus and Other Comorbidities	26	6.50	5	5.00	21	7.00
Hypertension and Other Comorbidities	52	4.00	15	4.00	37	4.00
Other Comorbid	92	4.00	28	6.00	64	3.50

Note: The normality test uses the Shapiro-Wilk test for statistical analysis since the sample per comorbid group is less than 50

Table 3. Length of Hospital Stay by Outcome in Each Comorbid Category

Comorbid Categories	Length of Hospital Stay (Days)					
	Total		Hospital discharge		Death	
	N	Median	N	Median	N	Median
No Comorbid	74	9.00	22	13.50	52	7.50
Diabetes Mellitus Only	37	9.00	5	15.00	32	7.50
Hypertension Only	39	8.00	16	12.50	23	6.00
Diabetes Mellitus and Hypertension	27	9.00	6	13.50	21	4.00
Diabetes Mellitus and Hypertension plus Other Comorbidities	31	6.00	8	14.00	23	5.00
Diabetes Mellitus or Hypertension plus Other Comorbidities	78	7.00	20	12.00	58	5.00
Diabetes Mellitus and Other Comorbidities	26	8.0	5	12.00	21	7.00
Hypertension and Other Comorbidities	52	5.50	15	12.00	37	5.00
Other Comorbid	92	5.00	28	15.00	64	4.00

For patients with death outcomes, those without any comorbidities and those with only diabetes mellitus had the longest stays, averaging 7.5 days. Conversely, the shortest hospital stays were observed in patients with both diabetes mellitus and hypertension and patients with other comorbidities (excluding diabetes and hypertension), with a median of 4 days (Table 3).

The data that has been collected was carried out by the Saphiro-Wilk normality test and found that not all variable data on the length of hospitalization in Intensive Care Units and hospitals have a significance value of  $P > 0.05$ , so it is necessary to carry out non-parametric statistical analysis with the Kruskal-Wallis Test. The results of the Kruskal-Wallis test on patients discharged from the hospital obtained insignificant results ( $P > 0.05$ ). However, in deceased patients, significant results were obtained ( $P < 0.05$ ), so the Dunn test was carried out as a follow-up test.

## DISCUSSION

The results showed that most patients were under 60 was in line with research in the United States, where the trend shifted to a younger age.<sup>9</sup> In addition, the study was dominated by men. This finding was also obtained in the research of Honardoost et al and Al-Salameh et al.<sup>8,9</sup> However, it differs from Wu et al's research, which had a greater proportion of female patients.<sup>10</sup>

A total of 80.4% of patients had comorbidities with a total of 10.3% having hypertension only and 9.8% having diabetes mellitus only. This differs from the study conducted on patients treated in ICU in Italy by Grasselli et al.<sup>11</sup>

In Grasselli's study, 67.4% of patients had comorbidities, hypertension as much as 41%, and diabetes mellitus as much as 12.8%.<sup>11</sup> The data of this study was taken from intensive care unit data, where the severity of these patients fell into the severe and critical categories; as many as 72.2% of patients died. This number is higher than Macedo's study, which had a 40.5% mortality rate in critical COVID-19 cases.<sup>12</sup>

The study found that patients without any underlying health conditions had the longest stay in the ICU, lasting up to 8 days. On the other hand, patients with comorbid diabetes mellitus or hypertension, along with other health conditions, had the shortest hospitalization period.<sup>13-15</sup> However, despite previous studies suggesting that the number of comorbidities affects the length of hospital stay, this particular study did not find any significant difference in hospitalization duration between patients with and without comorbidities.

Diabetes mellitus has chronic inflammatory characteristics that cause immunological response disorders, where the patient's innate and humoral immunity is suppressed. This is due to hyperglycemia can induce oxidative and inflammatory stress.<sup>16,17</sup> Individuals diagnosed with diabetes tend to have higher levels of leukocytes and neutrophils, which can impact the severity of COVID-19 symptoms.<sup>18</sup>

Research conducted by Zaki, Alashwal, and Ibrahim indicates that individuals with diabetes mellitus are at an increased risk of experiencing severe complications such as Accute Respiratory Distress Syndrome (ARDS), multi-organ failure, and even death. Additionally, diabetes can hinder the functions of macrophages and lymphocytes, which can interfere with T-cell development and interferon-gamma production. This condition causes suppression of immune function.<sup>5</sup> On the other hand, viral infections can cause fluctuations in blood sugar, which can lead to exacerbation of diabetic complications so that the healing process becomes longer.<sup>10</sup>

Individuals who suffer from chronic hypertension may encounter notable impairment of their endothelial function, which can further worsen their condition if they contract COVID-19. Furthermore, this may lead to a higher likelihood of COVID-19 complications.<sup>19</sup> Individuals who contract COVID-19 and suffer from hypertension are more likely to require intensive care. According to Huang et al, patients with hypertension tend to have higher levels of leukocytes, neutrophils, and D-dimer compared to those without hypertension. However, the study found no significant differences in length of

hospitalization and mortality among groups with hypertension and without hypertension.<sup>20</sup>

The shorter length of ICU stay in patients with comorbid diabetes mellitus or hypertension plus other comorbidities in this study was thought to be due to the protective impact of the drugs used by the patients. So that patient improvements can occur faster and impact a faster duration of intensive care. This may explain why patients without comorbidities with out-of-hospital outcomes have longer stays.<sup>16</sup>

In the case of COVID-19 treatment in the intensive care unit, ideally, patients with comorbid diabetes mellitus get insulin therapy through intravenous infusion. In addition to lowering blood glucose, insulin also has an anti-inflammatory effect. The benefits of this insulin can appear 2 hours after the infusion comes in and will continue to work as long as the patient is given an insulin infusion. Administration of insulin can result in the suppression of ROS and some chemokines. In addition, the drug also inhibits the process of thrombosis, and platelet aggregation, and induces thrombolysis.<sup>16</sup>

This can improve the general condition of the patient- because, in COVID-19 patients, there can be an increase in D-dimer, which is also said to be related to the lengthening of the patient's stay period.<sup>15,19</sup> Insulin is also a vasodilator down to the microvascular level. So insulin can potentially maintain blood flow and perfusion to various organ systems.<sup>16</sup>

In general, oral antidiabetics have more or less the same protective effects between groups. Its function to control glycemic levels causes reduced inflammation, endothelial injury, and viral proliferation. Several drugs such as DPP-4 inhibitor, GLP-1Ra, metformin, and pioglitazone also have immunomodulatory effects and reduce the risk of cytokine storms, reducing mortality rates.<sup>21-24</sup> The use of SGLT-2 inhibitor is debatable because of its side effects such as dehydration and the risk of diabetic ketoacidosis.<sup>21</sup>

However, recent studies have shown that SGLT-2 inhibitor is protective against SARSCoV-2 infection and COVID-19 hospitalization, hence reducing mortality and severity of COVID-19. This is

thought to be due to its cardioprotective effects.<sup>23</sup> Some debates still occur regarding the use of Pioglitazone because it is said that this drug can cause upregulation of Angiotensin Converting Enzyme 2 (ACE 2) expression, and its side effects are fluid retention.<sup>22</sup>

There is ongoing debate about the use of antihypertensive drugs for COVID-19 patients with hypertension. The use of Angiotensin Converting Enzyme Inhibitors (ACEi) and Angiotensin II Receptor Blockers (ARB) is believed to increase ACE 2 expression, which may put patients at greater risk of contracting COVID-19. However, ACE2 also can convert Angiotensin II to Angiotensin 1-7, which can bind to the Mas receptor and help with the apoptosis of anti-alveolar epithelial cells, lower blood pressure, and protect the endothelium. An increase in ACE 2 can also lead to vasodilation and an anti-inflammatory response, which can reduce lung damage severity and prevent ARDS.<sup>20</sup> According to studies by Braude et al and Jang et al, the use of ACEi or ARBs may reduce the duration of hospital stays for patients. However, researchers have yet to determine the exact mechanism behind this effect.<sup>13,25</sup>

The longest length of hospitalization in patients with out-of-hospital outcomes was found in the comorbid group of diabetes mellitus only and comorbidities other than diabetes mellitus and hypertension. At the same time, the shortest length of hospitalization is seen in patients with comorbid diabetes mellitus or hypertension plus other comorbidities. In the study, there was no significant difference in the length of hospitalization between comorbidities in patients and outcomes. The length of hospitalization of patients with comorbidities other than diabetes mellitus and hypertension is suspected to occur due to the severity of the patient's condition due to comorbidities, so it takes longer for the healing phase.

Research data show that patients without comorbidities and patients who have comorbid diabetes mellitus have the longest length of stay before the patient dies. In patients without comorbidities, this is suspected to occur due to the



absence of other diseases that worsen the patient's condition so that the patient can last longer. In patients with diabetes mellitus, the exact reason cannot be enforced because this study was not carried out to monitor the patient's blood sugar value, HbA1c, and the medicine taken. The longer length of stay in this comorbid group is thought to be due to antidiabetic drugs taken by the patient to have anti-inflammatory effects so that the patient can last longer.<sup>16</sup>

Patients with comorbidities other than diabetes mellitus and hypertension who die have a shorter hospital stay due to the severity of their condition. A study found that patients with comorbidities had a significantly different hospital stay length compared to those without comorbidities, those with hypertension alone, and those with diabetes mellitus alone.<sup>8</sup>

Other studies also show a significant correlation between comorbidities, especially cerebrovascular diseases, and the severity of COVID-19. The severity of the disease affects the hospital stay length, the need for intensive care, and mortality. Comorbidities such as cardiovascular disease, chronic lung disease, cancer, diabetes, and hypertension also affect the patient's condition severity. COVID-19 patients with comorbid cardiovascular disease may experience COVID-19-induced heart injury, while those with malignancies have a higher risk of severe COVID-19 due to the malignancy and treatment affecting their immune system.<sup>8</sup>

According to numerous studies, there is a strong link between hypertension and the severity of COVID-19. Hypertension significantly raises the risk of mortality and the likelihood of being admitted to the ICU.<sup>8,20,26</sup> Blood pressure control is an essential indicator of the progressiveness of COVID-19. Increased blood pressure was found to be associated with an increasingly bad outcome.<sup>26</sup>

Studies have shown that individuals with both COVID-19 and hypertension have a higher chance of mortality. It is believed that cytokine storms, caused by an imbalance of cytokines, contribute to this condition. This can affect the patient's improvement.

Additionally, an imbalance in the renin-angiotensin system can occur due to cytokine imbalances and excessive inflammation in hypertensive patients. This can lead to cell damage and worsen lung damage in COVID-19.<sup>20</sup>

It was found that obesity can also cause worsening of the condition in COVID-19 patients and can increase up to 2.3 times the risk of COVID-19 patients experiencing exacerbations. The mechanism of aggravation is caused because obesity followed by metabolic syndrome can cause organ disorders. In addition, in obese patients, there was also an increase in the expression of ACE2, which caused patients to be more susceptible to the virus.<sup>27</sup>

In the case of obesity, an immune response and an inflammatory response are too active, which can result in an excessive inflammatory response when exposed to COVID-19. In addition, obese patients will have limited chest movement and expansion due to increased abdominal pressure. This can adversely affect the patient's respiration compensation function, so the patient will more easily fall into respiratory failure.<sup>27</sup>

The results of the analysis of the length of hospitalization in intensive care rooms in patients with death outcomes found significant differences in the length of hospitalization between patients who had comorbidities other than diabetes mellitus and hypertension with patients without comorbidities, comorbidities other than diabetes mellitus and hypertension with only hypertension, comorbidities other than diabetes mellitus and hypertension with only diabetes mellitus. As already explained, this difference can be caused by comorbidities other than diabetes mellitus and hypertension can aggravate the patient's condition through therapy given for comorbidities, inflammatory and immune effects that are disturbed, as well as anatomical changes.<sup>8,27</sup>

As far as researchers know, there are no studies that discuss how having both diabetes mellitus and hypertension at the same time affects COVID-19 patients' severity. The authors believe that the reason patients with both conditions spend less time in the hospital could be due to more system

abnormalities in their bodies, which worsen their COVID-19 infection and lead to quicker death.

## LIMITATION

The shortcomings and weaknesses contained in this study include no recording of laboratory results, drugs used by patients both before and when treated, no calculation of the number of comorbidities suffered by patients, and no recording of suspected disease onset to the day of hospital admission so researchers cannot describe the progressiveness of the disease and the length of hospitalization adequately.

## CONCLUSION

After analyzing the data, it was determined that severe and critical COVID-19 patients who were treated at Saiful Anwar Hospital's ICU in Malang City between August 2020 and 2021 had the longest hospital stays when they did not have any other medical conditions and when they had only diabetes mellitus (Median=7.5 days). On the other hand, patients with comorbidities other than diabetes mellitus and hypertension had the shortest stays (Median=3.5 days). These findings were particularly significant for patients who did not survive.

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