# THE EFFECT OF TYPE 2 DIABETES ON THE DURATION OF RECOVERY OF COVID-19 PATIENTS IN BOGOR CITY REGIONAL GENERAL HOSPITAL

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**ABSTRACT**

Diabetes (36.5%) is the second most common comorbidity suffered by COVID-19 patients after hypertension (49.8%) in Indonesia. COVID-19 patients with diabetes have a 52.1% higher risk of being hospitalized. This study aims to determine the effect of diabetes on the recovery time of COVID-19 patients since being admitted to the hospital. A retrospective cohort study was conducted on 339 confirmed RT-PCR SARS-CoV-2 patients. The Cox Proportional Hazard regression test was used to analyze the relationship between diabetes and the length of recovery for COVID-19 patients. The survival probability for a COVID-19 patient without diabetes to recover from hospital stay for more than 12 days is 19.3% and 32.6% for diabetic patients. The median survival to recovery in patients without diabetes was 9 days (95% CI 8.56-9.44), whereas in patients with diabetes it was 10 days (95% CI 8.94-11.06). The average length of recovery needed for COVID-19 patients without diabetes was 13.13 days, and 20.38 days for COVID-19 patients with diabetes. Multivariate analysis showed no significant correlation between diabetes and recovery time with p-value = 0.302 (HR 1.216; 95% CI 0.839 – 1.762). COVID-19 patients with diabetes have a longer median recovery time than patients without diabetes. However, there is no significant relationship between diabetes and recovery time.

**Keywords**: COVID-19, diabetes, hospitalization, length of stay

## INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19) and was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020 (1,2). This virus has infected more than 500 million people and caused 6.4 million deaths worldwide (3). In Indonesia, as many as 6,267,137 people have been infected with this virus and it is estimated that this number will continue to grow (4).

The recovery time for COVID-19 patients depends on the patient's condition. A study in Eastern Ethiopia showed the average length of stay for COVID-19 patients was 12 days (IQR 8–17 days) (5). Research in Papua shows that the average length of stay for COVID-19 patients is 11 days (6). According to the Riau Provincial Health Office, the average time it takes a COVID-19 patient to be hospitalized is 7–10 days (7).

Comorbidities are often associated with a poor prognosis for the severity and mortality of COVID-19 patients (8). Patients with comorbidities have worse COVID-19 outcomes than patients without comorbidities. The presence of comorbidities reduces the cure rate by 44% compared to patients without comorbidities (9). This may be related to the prognosis of SARS-CoV-2 virus infection. COVID-19 patients with a history of hypertension, obesity, chronic pulmonary disease, diabetes, and cardiovascular disease have the worst prognosis and most often end up with deteriorating conditions such as acute respiratory distress syndrome (ARDS) and pneumonia (10). Diabetes mellitus (36.5%) is the second most common comorbidity suffered by COVID-19 patients after hypertension (49.8%) in Indonesia (4). COVID-19 patients with diabetes have a 52.1% higher risk of being hospitalized (11). Diabetes mellitus patients are known to have severe COVID-19 infection rates with poor outcomes. SARS-CoV-2 infection can inhibit glycemic control in diabetic

patients (12).

Research related to factors that affect the recovery time for COVID-19 patients is crucial during a pandemic to prevent excess patient capacity in terms of the availability of beds, medicines, and health workers. There have been many studies related to mortality in COVID-19 patients, but research related to factors that affect the recovery time for COVID-19 patients is still very limited. This study aims to determine the effect of diabetes on the recovery time of COVID-19 patients at Bogor City Regional General Hospital using a survival analysis approach.

## METHOD

This study is a quantitative analytic study using a retrospective cohort study design. The source population in this study were COVID-19 patients who had a history of type 2 diabetes mellitus, who were hospitalized between January – December 2021 in Bogor City Regional General Hospital. The medical record of patient data at the Bogor City Hospital has not been recorded in a computerized manner. There were 339 respondents who met the eligibility criteria included in this study from 374 respondents who were randomly selected by the medical record officer. The inclusion criteria in this study were COVID-19 patients aged >17 years who had information on the dates of admission and discharge from the hospital based on the recommendation from the clinician. While the exclusion criteria in this study were patients who died and pregnant women.

Data collection included characteristics of patients (age and gender), history of diabetes, history of hospitalization in the Intensive Care Unit (ICU), history of using a ventilator, and complications. Length of stay of hospitalization is defined as the time interval between patient's admission to discharge from the hospital due to clinician's recommendation. Starting from the date of entry until the date of discharge (getting permission from the doctor in charge of the patient) for the COVID-19 patient from the Bogor City Regional General Hospital. Length of Stay is classified into ≤12 days (event) and >12 days (censor). Patients discharged at their own request were classified as censors (7 patients).

Survival analysis using the Kaplan-Meier method was used to examine the median Length of Hospitalization Stay of hospitalization of COVID-19 patients with and without diabetes in Bogor City Regional General Hospital, as well as the cumulative survival probability. The log-rank test was employed to test the difference in survival time (length of hospitalization) between those with versus without diabetes. Multivariate analysis was done using Cox Proportional Hazard regression based on causal model. All potential confounders were analyzed in the full model and then removed one by one using backward elimination method to get a fit model.

This research has been approved by the Ethics Commission of the Bogor City Regional General Hospital Number 019/KEP-RSUD/EC/VIII/2022.

## RESULTS AND DISCUSSION

There are 2,269 COVID-19 patients at the Bogor City Regional General Hospital. Diabetes is the most common disease suffered by COVID-19 patients at Bogor City Regional General Hospital (18.3%). Of the 374 patients randomly selected in this study, 35 patients were excluded from the study (23 died (6.1%) and 12 were pregnant (3.2%)). Thus, the total sample in this study was 339 (90.6%) samples. Most samples are older than 45 years old (68.7%) with a median age of 53 (18 ± 90) years. The distribution of patients by sex in this study was male (51%) and female (49%). There are 28% of COVID-19 patients with diabetes and 72% without diabetes.

Based on Figure 1, it can be seen that the cumulative survival probability for COVID-19 patients is 0.231 or 23.1% to recover within ≤12 days. The median length of recovery was 10 days with 95% CI 9.6 days – 10.4 days. The average length of recovery is 16 days with 95% CI 15.2 days – 18.5 days. Figure 2 shows the cumulative survival probability for patients without diabetes is 19.3% and 32.6% for patients with diabetes for recovery time ≤12 days. Therefore, the curve of

the diabetic patient is above the curve of the patient without diabetes. Median survival to recovery in patients without diabetes was 9 days (95% CI 8.56–9.44), whereas in patients with diabetes it was 10 days (95% CI 8.94–11.06). The average recovery time for patients without diabetes was 13.13 days, and 20.38 days for COVID-19 patients with diabetes.

This result is in line with research by Wu et al. (2020) which stated that COVID-19 patients with diabetes had a longer hospitalization stay of 3.2 days than patients without diabetes (13). In line with the research of Bode et al. who stated that the median length of stay was longer in patients with uncontrolled diabetes or hyperglycemia compared with patients without diabetes or hyperglycemia (5.7 vs 4.3 days, P < 0.001) (14). Research by Liu et al. demonstrated a lower cumulative survival probability in patients with diabetes compared with patients without diabetes to death (15). Research by Lampasona et al. also demonstrated a lower cumulative survival probability in patients with diabetes compared with patients without diabetes to death (16).

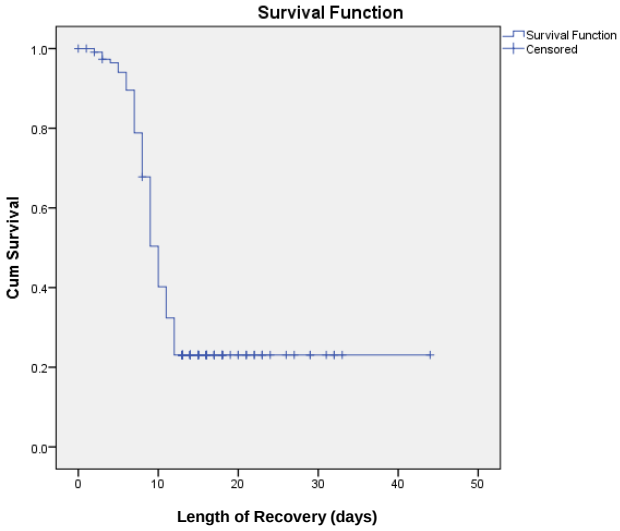


Figure 1. Cumulative Survival Probability Curve of COVID-19 patients

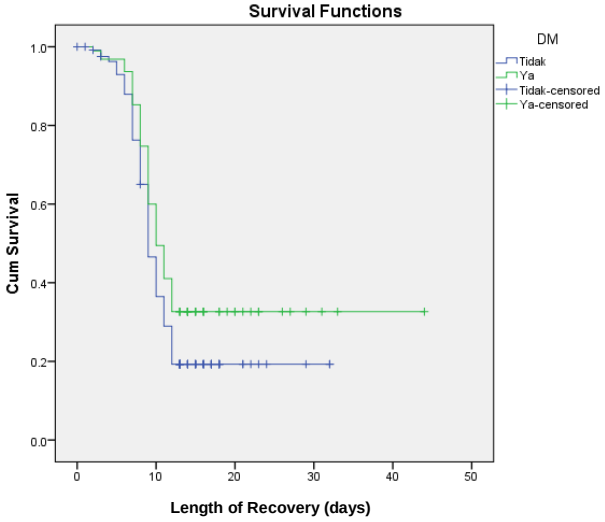


Figure 2. Cumulative Survival Probability Curve of COVID-19 patients by Diabetes Status

This study found that the hazard rate in patients without diabetes is greater than hazard rate in patients with diabetes to be treated for ≤12 days (1.65 vs 1.12). This means that patients with

diabetes are more likely to recover longer than 12 days. It can be seen that the smallest cumulative survival probability value is owned by patients who did not need a ventilator during treatment (0.077 or 7.7%). This means that patients who did not need a ventilator during treatment are more likely to recover faster. Judging from the hazard rate, patients who did not need a ventilator during treatment had a greater chance of recovering ≤12 days than patients who needed a ventilator during their treatment (2.56 vs. 1.35). Based on the results of the log rank test, it is known that only gender, Length of symptoms onset until hospital admission, pneumonia, and cough have a p-value >0.05. So, it can be interpreted that there is no significant difference in the probability of survival in these variables (Table 1).

**Table 1. Proportion, Kaplan-Meier Cumulative Survival Probability, and Hazard Rate of COVID-19 Patients According to Length of Stay**

| Variables | Length of Recovery | | Cumulative Survival Probability | Log Rank Test p-value | Hazard Rate |
|---|---|---|---|---|---|
| | >12 days (%) *Censor* | ≤12 days (%) *Event* | | | |
| **Overall** | **82 (24.2)** | **257 (75.8)** | **0.231** | | **1.47** |
| **Diabetes** | | | | | |
| No | 51 (20.9) | 193 (79.1) | 0.193 | **0.007** | 165 |
| Yes | 31 (32.6) | 64 (67.4) | 0.326 | | 1.12 |
| **Age** | | | | | |
| <45 years | 18 (17.0) | 88 (83.0) | 0.154 | **0.001** | 1.87 |
| ≥45 years | 64 (27.5) | 169 (72.5) | 0.266 | | 1.32 |
| Gender | | | | | |
| Female | 46 (27.7) | 120 (72.3) | 0.255 | 0.126 | 1.37 |
| Male | 36 (20.8) | 137 (79.2) | 0.208 | | 1.57 |
| Length of symptoms onset until admission | | | | | |
| 0–4 days | 46 (24.3) | 143 (75.7) | 0.228 | 0.963 | 1.48 |
| 5–9 days | 29 (23.4) | 95 (76.6) | 0.228 | | 1.48 |
| >9 days | 7 (26.9) | 19 (73.1) | 0.269 | | 1.31 |
| Severity | | | | | |
| Mild | 4 (12.9) | 27 (87.1) | 0.100 | **<0.001** | 2.30 |
| Moderate | 14 (11.6) | 107 (88.4) | 0.101 | | 2.29 |
| Heavy | 3 (15.8) | 16 (84.2) | 0.111 | | 2.19 |
| Critical | 61 (36.3) | 107 (63.7) | 0.360 | | 1.02 |
| Number of comorbidities | | | | | |
| No comorbid | 23 (84.9) | 129 (15.1) | 0.128 | **<0.001** | 2.06 |
| 1 comorbid | 29 (33.0) | 59 (67.0) | 0.330 | | 1.11 |
| >1 comorbidities | 30 (30.3) | 69 (69.7) | 0.297 | | 1.21 |
| Hypertension | | | | | |
| No | 50 (21.9) | 178 (78.1) | 0.205 | **0.008** | 1.58 |
| Yes | 32 (28.8) | 79 (71.2) | 0.283 | | 1.26 |
| Cardiovascular Disease | | | | | |
| No | 54 (21.4) | 198 (78.6) | 0.202 | **0.008** | 1.59 |
| Yes | 28 (32.2) | 59 (67.8) | 0.315 | | 1.16 |
| Chronic Kidney Disease | | | | | |
| No | 74 (23.2) | 245 (76.8) | 0.220 | **0.019** | 1.51 |
| Yes | 8 (40.0) | 12 (60.0) | 0.400 | | 0.92 |
| Pneumonia | | | | | |
| No | 13 (25.5) | 38 (74.5) | 0.227 | 0.811 | 1.48 |
| Yes | 69 (24.0) | 219 (76.0) | 0.232 | | 1.46 |

| Variables | Length of Recovery | | Cumulative Survival Probability | Log Rank Test p-value | Hazard Rate |
|---|---|---|---|---|---|
| | >12 days (%) *Censor* | ≤12 days (%) *Event* | | | |
| Acute respiratory distress syndrome | | | | | |
| No | 36 (13.7) | 226 (86.3) | 0.124 | **<0.001** | 2.09 |
| Yes | 46 (59.7) | 31 (40.3) | 0.593 | | 0.52 |
| Acute Kidney Injury | | | | | |
| No | 70 (22.2) | 246 (77.8) | 0.209 | **0.002** | 1.57 |
| Yes | 12 (52.2) | 11 (47.8) | 0.522 | | 0.65 |
| Hypercoagulation | | | | | |
| No | 28 (16.0) | 147 (84.0) | 0.136 | **<0.001** | 1.99 |
| Yes | 54 (32.9) | 110 (67.1) | 0.329 | | 1.11 |
| Fever on admission | | | | | |
| No | 65 (77.8) | 228 (22.2) | 0.211 | **0.028** | 1.56 |
| Yes | 17 (37.0) | 29 (63.0) | 0.358 | | 1.03 |
| Cough | | | | | |
| No | 21 (28.8) | 52 (71.2) | 0.268 | 0.165 | 1.32 |
| Yes | 61 (22.9) | 205 (77.1) | 0.221 | | 1.51 |
| Hard to breathe | | | | | |
| No | 17 (16.2) | 88 (83.8) | 0.147 | **0.004** | 1.92 |
| Yes | 65 (27.8) | 169 (72.2) | 0.268 | | 1.32 |
| ICU admission | | | | | |
| No | 58 (18.9) | 249 (81.1) | 0.176 | **<0.001** | 1.74 |
| Yes | 24 (75.0) | 8 (25.0) | 0.750 | | 0.29 |
| Use of ventilators | | | | | |
| No | 5 (9.4) | 48 (90.6) | 0.077 | **0.001** | 2.56 |
| Yes | 77 (26.9) | 209 (73.1) | 0.259 | | 1.35 |

COVID-19 patients with diabetes have a 52.1% higher risk of being hospitalized (11). Diabetes mellitus patients are known to have severe COVID-19 infection with poor outcomes. SARS-CoV-2 infection can inhibit glycemic control in diabetic patients. Several studies have found an association between diabetes and acute respiratory distress syndrome (ARDS), coronary care unit (CCU) admission, and death in patients with COVID-19 (12).

Elevated glucose levels directly enhance SARS-CoV-2 replication, and glycolysis sustains SARS-CoV-2 replication through production of mitochondrial reactive oxygen species and activation of hypoxia triggering factor 1α (HIF-1α). Therefore, hyperglycemia can support viral proliferation. Consistent with this assumption, hyperglycemia or a history of type 1 and type 2 diabetes mellitus was found to be an independent predictor of morbidity and mortality in patients with SARS-CoV-2 (17).

Table 2 shows the Hazard Ratio (HR) of diabetes to the length of recovery for COVID-19 patients at Bogor City Regional General Hospital. It can be seen that the HR for diabetes has a value of <1 (0.705; 95% CI 0.531–0.936). That is, diabetes is less likely to resolve within ≤12 days and more likely to resolve >12 days. The proportional hazard assumption test has been carried out and it is known that all variables meet this assumption. Table 3 shows the full model for determining confounding variables.

After being analyzed by looking at the difference between HR crude and HR adjusted, the final model was obtained as shown in table 3. It can be seen that only the number of comorbidities and ARDS was a confounder in this study with an ΔHR value >10%. The HR value in the final model for diabetes was 1.216 with a 95% CI 0.839 – 1.762 (p-value = 0.302).

This research is in line with the study by Baihaqi and Rumaropen (2022) which showed that there was no significant relationship between diabetes and the length of stay of COVID-19 patients

[p-value = 0.509 (OR 0.63; 95% CI 0.16-2.45)] (6). In line with the research by Seyed Alinaghi et al. (2021) which did not show a significant association between diabetes and prolonged recovery time in COVID-19 patients [p-value = 0.31 (AOR 1.40; 95% CI 0.73–2.66)] (18). Research by Guo et al. (2021) also showed that there was no significant relationship between diabetes and the length of stay of COVID-19 patients [p-value = 0.63 (OR 0.71; 95% CI 0.16–2.91)] (19).

**Table 2. Cox Proportional Hazard Regression Analysis for the Effect of Type 2 Diabetes, and All Other Covariates, on Length of Recovery for ≤12 Days**

| Variables | Hazard Ratio (95% CI) | P-value |
|---|---|---|
| **Diabetes** | | |
| No | Ref. | |
| Yes | 1.203 (0.659 – 2.195) | 0.547 |
| Age | | |
| <45 years | Ref. | 0.320 |
| ≥45 years | 0.856 (0.630 – 1.163) | |
| Gender | | |
| Female | Ref. | 0.068 |
| Male | 1.279 (0.982 – 1.666) | |
| Length of symptoms onset until admission | | |
| 0–4 days | Ref. | 0.160 |
| 5–9 days | 1.166 (0.883 – 1.540) | 0.280 |
| >9 days | 1.617 (0,963 – 2.715) | 0.069 |
| Severity | | |
| Mild | Ref. | 0.330 |
| Moderate | 0.701 (0.325 – 1.512) | 0.365 |
| Heavy | 0.870 (0.346 – 2.187) | 0.767 |
| Critical | 1.146 (0.468 – 2.806) | 0.766 |
| Number of comorbidities | | |
| No comorbid | Ref. | 0.475 |
| 1 comorbid | 0.754 (0.403 – 1.410) | 0.376 |
| >1 comorbidities | 0.801 (0.231 – 2.782) | 0.727 |
| Hypertension | | |
| No | Ref. | 0.862 |
| Yes | 0.944 (0.494 – 1.804) | |
| Cardiovascular Disease | | |
| No | Ref. | 0.826 |
| Yes | 0.937 (0.526 – 1.669) | |
| Chronic Kidney Disease | | |
| No | Ref. | 0.215 |
| Yes | 0.598 (0.266 – 1.347) | |
| Pneumonia | | |
| No | Ref. | 0.772 |
| Yes | 1.100 (0.577 – 2.100) | |
| Acute respiratory distress syndrome | | |
| No | Ref. | <0.001 |
| Yes | 0.418 (0.257 – 0.678) | |
| Acute Kidney Injury | | |
| No | Ref. | 0.555 |
| Yes | 0.820 (0.424 – 1.584) | |
| Hypercoagulation | | |
| No | Ref. | 0.027 |
| Yes | 0.578 (0.357 – 0.938) | |
| Fever on admission | | |
| No | Ref. | 0.254 |

| Variables | Hazard Ratio (95% CI) | P-value |
|---|---|---|
| Yes | 0.788 (0.523 – 1.186) | |
| Cough | | |
| No | Ref. | 0.848 |
| Yes | 1.033 (0.744 – 1.433) | |
| Hard to breathe | | |
| No | Ref. | 0.953 |
| Yes | 1.009 (0.761 – 1.337) | |
| ICU admission | | |
| No | Ref. | 0.004 |
| Yes | 0.326 (0.154 – 0.693) | |
| Use of ventilators | | |
| No | Ref. | 0.537 |
| Yes | 0.890 (0.614 – 1.289) | |

**Table 3. Final Model for Cox Regression Analysis for Hospitalization for 12 Days or Less**

| Variables | B | SE | HR (95% CI) | P-value |
|---|---|---|---|---|
| Diabetes | 0.196 | 0.189 | 1.216 (0.839 – 1.762) | 0.302 |
| Number of Comorbidities | | | | |
| No Comorbid | - | - | Ref. | 0.005 |
| 1 Comorbid | -0.483 | 0.170 | 0.617 (0.443 – 0.860) | 0.004 |
| >1 Comorbidities | -0.522 | 0.194 | 0.593 (0.405 – 0.868) | 0.007 |
| Acute Respiratory Distress Syndrome | -1.240 | 0.197 | 0.289 (0.197 – 0.426) | <0.001 |

The recovery time for COVID-19 patients is influenced by many factors. Researchers conducted a sub-analysis to find out the factors that most influenced the recovery time for COVID-19 patients at Bogor City Regional General Hospital. Based on the results of the analysis, it is known that the factors most related to the length of recovery for COVID-19 patients at Bogor City Regional General Hospital are ARDS, admission to the ICU during hospitalization, hypercoagulability, and the number of comorbidities. Infection with the SARS-CoV-2 virus can trigger an abnormal systemic inflammatory response due to excessive production of proinflammatory cytokines and chemokines, or an event often called a cytokine storm, which is a feature of ARDS caused by COVID-19 infection (20). Men, obesity, old age, smoking, dyspnea, diabetes and hypertension have a higher risk of developing ARDS in COVID-19 patients (21,22). Cytokine storms can also cause systemic inflammatory response syndrome. Consequently, activation of coagulation increases and causes hypercoagulation, which increases the risk of micro and macro thrombosis (23,24).

It is possible that the results in this study were influenced by chance variation seen from the confidence interval that passed the null value (95% CI 0.839 – 1.762). There are several reasons why diabetes did not affect the time to recover from COVID-19 infection in this study. The first possibility is that COVID-19 patients with diabetes do not affect the healing time >12 days because glucose levels were controlled as a result of a low-sugar diet that was intervened in the hospital. The second possibility is based on several studies showing a high risk of death in COVID-19 patients with diabetes (25–27). Whereas in this study the samples taken were patients who had successfully recovered from COVID-19 infection, so there is a possibility that the patients in this study were patients with controlled diabetes. Another possibility is that there is an influence on the recovery time of other COVID-19 patients who were not analyzed in this study.

To reduce morbidity and mortality from SARS-CoV-2 infection, it is important to ensure that all those infected patients are receive appropriate health care. To achieve this, excess capacity such as the need for beds, medicines and medical personnel in the hospital sector must be prevented. Many studies have been conducted regarding the effects of diabetes on poor outcomes and even death in COVID-19 patients, but research on its effect on the time to recover from COVID-19 infection in COVID-19 patients is still very limited. The length of time it takes for

COVID-19 patients to be hospitalized is very important in determining the availability of the beds needed to prevent overcapacity of patients and the ability of regions to cope with the pandemic. The results of this study did not find any relationship between diabetes and length of recovery, but the results of the sub-analysis found that patients who experienced ARDS and hypercoagulability, required intensive care, and had one or more comorbidities related to the length of time to recover from COVID-19 infection. So that this research can be used as reference material for health workers in prioritizing patients with this risk.

Cohort studies have limitations in dealing with rare outcomes. This study was taken from manual medical record data that had not been computerized, so data collection was difficult due to the large number of samples. This study also did not take into account drug interventions used in COVID-19 patients, clinical pathways, vaccination status, and hospital regional policies. Suggestions for further research to take into account these variables.

## CONCLUSION

COVID-19 patients with diabetes have a longer median recovery time than patients without diabetes. However, there is no significant relationship between diabetes and recovery time. Based on the results of the survival analysis, it was found that diabetes, age ≥45 years, critical severity, had one or more comorbidities, had symptoms of fever and shortness of breath, had ARDS, acute kidney failure, hypercoagulable, was admitted to the ICU during treatment at the hospital, and required ventilators have a higher cumulative survival probability of having an illness-to-recovery time of ≤12 days. Advice to medical personnel to pay more attention to patients who have this risk. It is hoped that this research can serve as a guide for future researchers to consider drug use, clinical pathways, vaccination status, hospital policies, and other comorbidities that may affect the recovery time of COVID-19 patients.

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