Factors associated with time to recovery among COVID-19 patients in selected Zambian hospitals, 2020

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ABSTRACT

Background: It is important to understand the time and factors associated with recovery to help improve response to the COVID-19 healthcare-related challenges and also to enhance information management. As a result, proof of the length of time it takes to recover from COVID-19 is required to develop effective treatment and prevention approaches. This study estimated the duration to recovery and related parameters of COVID-19-infected patients in Zambia for cases diagnosed between March 18 and June 26, 2020. **Methods:** The retrospective study examined 705 patients admitted to the fourteen COVID-19 isolation hospitals across Zambia. All COVID-19 tests used the RT-PCR of nasopharyngeal swabs. Recovery is operationally defined as a patient who presented a negative COVID-19 test on day 14 and was considered to have recovered. The Akaike Information Criteria (AIC) and Bayesian information criteria (BIC) were used to fit parametric models and pick the best predictive model. **Results:** Median time to recovery in the quarantine facilities was found to be 12 days (IQR 10-17). Out of 705 patients, 535 (75.9%) recovered within the median days of 14 days while 170 (24.1%) did not recover within the 14 days. In the adjusted model, a year increase in age of patients delayed time to recovery by 0.4% (ATR: 1.004, 95%CI; 1.002, 1.007; p=0.001). Similarly, patients admitted with shortness of breath had a delayed time to recovery by a factor of 11.4% (ATR: 1.114, 95%CI; 1.018, 1.221; p=0.019) compared to those with no shortness of breath. **Conclusion:** Age and shortness of breath at admission were associated with longer hospital stay among COVID-19 patients. These factors should be considered by program managers while making plans and policy recommendations for improved service delivery.

KEYWORDS: Corona Virus, Survival Analysis, Parametric Model, Log-Logistic Regression Model

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Introduction

The COVID-19 disease global mortality rate is approximately 3.4 per 100,000 population, making it higher than that caused by most influenza virus strains [1]. Adult patients with underlying health conditions have been reported to be more susceptible to death from COVID-19 [2]. This risk of dying from COVID-19 increases further in the presence of one or more comorbidities [3].

There have been a few studies undertaken in Africa where the pandemic appears to be distinct from that of other continents in terms of virus propagation speed and mortality toll [4]. Case fatality rates have been 3.9 per cent worldwide, 7.1 per cent in Europe, 4.0 per cent in North America, 3.5 per cent in South America, and 2.1 per cent in Africa, with the most affected regions being South America, North America, and Europe [5]. Despite being the world's second most populous continent, with an estimated 17.2 per cent of the world's population, Africa accounts for only 5 per cent of total cases and 3 per cent of overall mortality as of August 1, 2020, when compared to other continents [4,6,7]. However, this could be due to underreporting [8], weak health systems coupled with high levels of poverty and inequalities in many of the countries [9].

On March 18, 2020, Zambia recorded its first COVID-19 case and by 21st May 2020, there were a total of 668 cases reported with 509 active cases, 152 (22.75%) recoveries and 7 (1.05%) deaths [10]. There is limited data on treatment outcomes of COVID-19 patients in Zambia, particularly on factors that determine recovery and discharge from hospitals or treatment centres [11]. Patients with COVID-19 in Zambia are managed from various hospitals and isolation facilities across the country. A study done in Ethiopia [3] on COVID-19 patients, determined the time from infection to negative conversion or recovery. Estimating the duration to recovery and the variables that influence recovery can aid in the formulation of preventative measures and the optimization of treatment. [3]. This study therefore assessed factors that determine time to recovery, from the time patients are admitted into care to the time they are discharged, at fourteen hospital isolation facilities in Zambia.

Methods

Study Design and Setting

This was a national hospital-based retrospective cohort study among COVID-19-positive patients admitted to 14 hospitals. The was considered to be the period between the initial positive test and the negative test at discharge. The observational period was 14 days; that is if a patient did not have a negative COVID-19 test on day 14 were considered to have not recovered and if they had a negative COVID-19 test on day 14 were considered to have recovered. The recovery time was arrived at using the Standard Operating Procedure (SOP) for the management of patients COVID-19 patients [12,13,14]. The study period was from 18th March to 26st May 2020 from the time the patients were admitted into care at the fourteen isolation facilities (Levy Mwanawasa Hospital, University Teaching Hospital, Chinsala general hospital, Nakonde district hospital, Kabwe Mine Hospital, Livingstone Central Hospital, Chipata Central Hospital, Lewanika general hospital, Mansa General Hospital, Masaiti Hospital, Ndola teaching hospital, Solwezi general, Lumwana district hospital and Kasama general hospital), to the time they recover.

Study Population and Data Source

All COVID-19-positive patients registered on the Health Management Information System (HMIS) registration book and had full information about the severity of their disease and other socio-demographic characteristics were included. They included a total of 747 patients and about 7(0.9%) with incomplete clinical and demographic data were excluded. The data was obtained from Zambia National Public Health Institute, the institute responsible for disseminating COVID-19 updates for the country.

Patients admitted at health facilities during the study period had their nasopharyngeal swabs tested with the Real-Time Polymerase Chain Reaction (RT-PCR) according to Zambia National COVID-19 guidelines which are in line with World Health Organisation recommendations [15]. Standard treatment for all patients in all the facilities was in line with the COVID-19 treatment protocol by the Ministry of Health [12].

Hospital records of patients were reviewed, and data was captured using a Microsoft Excel spreadsheet showing the date when patients were diagnosed, the date when the patient started treatment and when the patient was discharged. The primary dependent variable was time to recovery from COVID-19 whereas the explanatory variables were social demographic variables (age, gender), symptoms (fever, cough, sore throat, dyspnoea, headache, chest pain, nausea, vomiting), and co-morbidity (tuberculosis, HIV).

Statistical Analysis

The time to recovery was defined as the period between when patients were diagnosed positive for COVID-19 and when they were diagnosed negative by RT-PCR by two consecutive tests and were free of symptoms after admission to the hospital. The event was disease recovery, and patients who developed an event, died, or were transferred out of the study were censored.

The research population was described using descriptive statistics such as means, medians, interquartile ranges, percentages, frequencies, and standard deviations. Standard deviation (SD) was used to describe continuous variables for normally distributed variables. The Kaplan-Meier (KM) method was used to estimate recovery time from COVID-19, and the Log-rank test was utilized to compare survival times among categories of categorical factors. Before fitting the survival model, proportional hazard assumptions (PHA) were verified. To explore the relationships between continuous variables and the outcome, a Wilcoxon rank-sum test was used [16]. The study fitted multiple parametric models after PHA was not met for the best-fit model for the data in adjusted multivariable analysis. The models were fitted using Stata/MP version 14.2 (Stata Corporation, Texas, TX, USA), were Exponential, Weibull, Gompertz, Log-Logistic, Log-Normal, and Generalized Gamma and this has been reported elsewhere [17], Bayesian information criterion (BIC) were utilized to fit the best model. BIC is a criterion for model selection among a finite set of models [18]. Finally, the model with a lower number implies that the proposed model does well in fitting the data. The best-fitting survival model for the data was the log-logistic regression model. The accelerated failure time (AFT) family includes the Log-logistic distribution, which is useful for modelling non-monotone hazard rates [16,17]. The assumption underpinning testing many models was that the probability of recovery was not well understood, and therefore picking a model that fits well helps in understanding the recovery process and the factors that increase or decrease recovery among COVID-19 patients [11,19].

Operational Definition

Event: In this study period, refers to the recovery of COVID-19-positive patient

Length of stay: refers to the period, measured in days, between the date of the admission and the patient's discharge from the treatment facility [3].

Censored: refers to patients who did not have a negative outcome, who have died, who have been lost to follow-up, and who have only had home-based care [20].

Time to recovery is determined by calculating the difference (in days) between the commencement of therapy and recovery. It represents the number of days from patient admission to recovery from COVID-19 [20].

Co-morbidities: refers to people with COVID-19 who have health problems such as TB and HIV, before, during, or after being admitted to treatment centers [20].

Ethical considerations

The information was gathered from the Zambia National Public Health Institute (ZNPHI), which is part of the Zambian Ministry of Health and permission was granted by the institute. ZNPHI monitors and keeps data from all patients in all health facilities and publishes country situational reports which provide statistics on the evolution of COVID-19 in Zambia. ZNPHI as a statutory institution on its own, granted permission to access, analyse and publish information from its database. No primary data was collected for this study and any information that can be used to identify individuals was removed. Permission was obtained to use the secondary data from the Zambia National Public Health Institute for this research, which is the custodian of the COVID-19 data in Zambia.

Results

Clinical and demographic characteristics

At the end of the follow-up, 705 (95.3%) of the patients recovered from COVID-19, and 35 (4.7%) were censored. Among those censored instances, 10 (28.6%) were released by isolated home-based care following clinical improvement, 6 (17.1%) were lost to follow-up from the treatment center, and 19 (54.3%) passed away while receiving treatment. Of the 705 patients quarantined, 169 (24.0%) were females and 536 (76.0%) were males. At the time of diagnosis, the median age was 39 years (IQR 3-77). There were 535 (75.9%) recoveries within 14 days and 170 (24.1%) did not recover within fourteen days.

The median recovery time was 12 days (IQR 10-17) and the total person time at risk was 9078 days. Assuming the incident rate (i.e. hazard function) is constant; the incident rate of recovery was estimated at 0.059 per day (5.9%) or 59 per 1000 persons per day. For seven days, recovery rate was 0.93 (0.93%) with a 95% confidence interval of 0.90, - 0.94, fourteen days the recovery was 0.50 (50.0.0%) and the 95% confidence interval of 0.46 - 0.54.

During the follow-up period, that is the period from the initial positive COVID-19 test to the negative test at discharge, 412 (72.9%) recovered. The median age of patients who recovered from COVID-19 was 36 years (IQR = 30, 45) compared to those who did not recover at 45 years (IQR = 35, 56). Age (p=0.001) Fever (p=0.036), sore throat (p=0.001), and shortness of breath (p=0.015) were all associated with recovery (**Table 1**).

COVID-19 patients who presented with shortness of breath at diagnosis had lower recovery probability and this was statistically significant with p-value= 0.015. Below four days after diagnosis, patients in both groups had an equal probability of recovery, while from four days to the fourteenth day, the recovery between the two groups were different and the fourteenth day and beyond the two groups were different (**Figure 1**). COVID-19 patients who presented with sore throats at diagnosis had lower recovery probability and this was statistically significant (p-value= 0.001). Between days five and ten patients who had sore throats had lower probabilities of recovery, while from about the eleventh day, there was no difference in the recovery but after the thirteenth day probability of recovery seemed to have swapped between the two groups going forward (**Figure 2**).

Patients in the COVID-19 study who had a fever at the time of diagnosis had a greater chance of recovery, which was statistically significant (p-value=0.036). Below ten days after diagnosis, patients in both groups had an equal probability of recovery, while from day eleven and beyond recovery between the two groups was different (**Figure 3**).

Best fit Model

The model with the lowest value of the BIC was Log-Logistic and fit the data quite well. This implies that the risk of patients follows a Log-logistic function implying that risk exhibits a non-monotonicity hazard function that is it starts to increase in the early stage of the disease and later decreases (**Table 2**).

An unadjusted model, not adjusting for confounders, a year increase in age of patients delayed time to recovery by 0.5% (Time Ratio: 1.005, 95%CI; 1.002, 1.007; p=0.001); shortness of breath delayed time to recovery for in patients diagnosed with COVID-19 by 13.5% (Time Ratio: 1.004, 95%CI; 1.041, 1.240; p=0.001).

Further analysis using an adjusted Log-Logistic model showed that a year increase in age of patients delayed time to recovery by a factor of 0.4% (Adjusted Time Ratio: 1.004, CI 95%; 1.002, 1.007; p=0.001) holding all other factors constant. Likewise controlling for all other variables, patients who had presented with shortness of breath compared to those without had delayed time to recovery by a factor of 11.4% (ATR: 1.114, CI 95%; 1.018, 1.221; p=0.019). All the other factors examined both the unadjusted and adjusted models failed to predict the time to recovery of COVID-19 patients (**Table 3**).

Discussion

It is important to understand the time and factors associated with recovery to help health systems improve their response to COVID-19. Age and dyspnoea played a major influence in COVID-19 patients' delayed time to recovery, according to the results of the Log-Logistic model. Patients in the hospital were found to be discharged by 12 median days (IQR 10-17) after admission in this retrospective analysis. Comparable estimates have been reported in previous studies [21,22]. The relatively long time from onset of illness to hospital admission could be a factor in the longer onset to recovery time; the median time from onset of illness to hospital admission was 15 days (IQR 7.0-30.0), while the median time from onset of illness to hospital discharge was 30.0 days (IQR 21.5-43.0).

An increase in the age of COVID-19 patients significantly delayed the time to recover from COVID-19. Earlier reports noted that being of older age prolonged the time to recovery from COVID-19 [23]. Another study concluded that longer hospital stays were linked to inpatients aged 45 years and above [24].

The study also found that COVID-19 patients who presented with shortness of breath at diagnosis had delayed time to recovery. This could be due to the worsening severity of the cases with reported shortness of breath. The relationship between shortness of breath and recovery from COVID-19 has earlier been reported [24,25]. This study suggests that even among symptomatic individuals examined in outpatient settings, symptom relief and return to normal health could take weeks [26]. Oxygen levels dip as the viral load continues to increase causing more damage to the body's respiratory linings compromising functionality and breathlessness and low oxygen saturation can continue to occur, even after the virus diminishes from the body [27].

Major limitations were missing information on the patient's clinical records from the hospital where the patients were quarantined and hence limited observations in our study as a result; only patients with complete information were included. Another limitation was that the lack of commodities to do two tests at discharge.

Conclusion

The findings of the study show that older age patients were less likely to recover faster than younger patients. Therefore, patients of older age need more care, early detection and management can help to prevent the onset of serious illness of COVID-19. Also, patients who presented with dyspnoea need careful observation and interventions to avoid delay in recovery from COVID-19. To better respond to COVID-19-related difficulties and improve health information management, the health system must be strengthened. Modelling COVID-19 data was critical to better understand the elements that influence recovery time after COVID-19 infection by utilizing the best model that provided more accurate estimations.

What is known about this topic

- A notable percentage of persons with SARS-CoV-2 infection still had symptoms nearly two months after their diagnosis
- The log-logistic AFT model accurately described the recovery time of patients with COVID-19
- The median recovery time of patients with COVID-19 cases was long, and factors such as older age group, presence of fever, and comorbidity was an independent predictors of delayed recovery from COVID-19

What this study adds

- To better response to COVID-19-related difficulties and improve health information management, the health system must be strengthened
- Therefore, the patients with older age need more care, early detection and management can help to prevent the onset of serious illness of COVID-19
- Modelling COVID-19 data was critical in order to better understand the elements that influence recovery time especially in Africa set up after COVID-19 infection by utilizing the best model that provided more accurate estimations

Competing interests

There are no competing interests declared by the author(s). There is no sponsorship for this research. On request, the datasets used in or analyzed during the current work may be obtained from the corresponding author.

Authors' contributions

Conceptualization of the article: KM

Data Curation: KM, JS, MM, PS, NM, CM, MC.

Investigations and Methodology: KM, JS, MM, PJC, IF, RH, NS, AG, JMZ, MML, DS, PS, MC, NM, CM, SS

Data analysis and interpretation: KM, KM, PMZ, AN, JS, NS, JMZ, IF, DS, NK, MM, AG, KM, MML, PS, NM, CM, PMZ

Writing-original draft: KM KM, MC, PS, MM, NM, PJC, MML, NK, DS, VM, IF, NK, JMZ, AG, AN, NK, MML, PMZ, NS, KM, JMZ, DS, and SS read and approved the final document after reviewing it and providing written suggestions to improve the overall presentation of the results.

Tables and figures

Table 1: Demographic and clinical characteristics of 705 COVID-19 patients isolated at different hospitals in Zambia.

Table 2: Comparison of the BIC between Parametric Models

Table 3: Crude and Adjusted Time Ratios of the COVID-19 patients using the Log Logistic Model.

Figure 1: Estimates of the recovery time in days of COVID-19 patients

Figure 2: Estimates of the recovery time in days of COVID-19 patients

Figure 3: Estimates of the recovery time in days of COVID-19 patients

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Table 1: Demographic and clinical characteristics of 705 COVID-19 patients isolated in different hospitals in Zambia			
Factors	**Positive COVID-19 patients** (Total sample= 564)		**P-value**
	Recovered N= 535 (75.9%)	**Not recovered** N= 170 (24.1%)	
Age years, median (IQR)	36 years (30.45)	45 years (35.56)	0.001[W]
Gender			
Female	137 (25.6%)	32 (18.8%)	
Male	398 (74.4%)	138 (81.20%)	0.071[C]
Fever			
No	423 (79.1%)	143 (84.1%)	
Yes	112 (20.9%)	27 (15.9%)	0.036[C]
Cough			
No	307 (57.4%)	92 (54.1%)	
Yes	228 (42.6%)	78 (45.9%)	0.454[C]
Sore throat			
No	383 (71.6%)	126 (74.1%)	
Yes	152 (28.4%)	44 (25.9%)	0.001[C]
Dyspnoea			
No	417 (77.9%)	147 (86.5%)	
Yes	118 (22.1%)	23 (13.5%)	0.015[C]
Headache			
No	341 (63.7%)	100 (65.4%)	
Yes	60 (36.3%)	53 (34.6%)	0.819[C]
Chest Pain			
No	374 (69.9%)	125 (74.7%)	
Yes	161 (30.1%)	45 (26.5%)	0.366[C]
Nausea			
No	400 (74.8%)	127 (74.7%)	
Yes	135 (25.2%)	43 (25.2%)	0.987[C]
Vomiting			
No	438 (81.9%)	144 (84.7%)	
Yes	97 (18.1%)	26 (15.3%)	0.396[C]
Tuberculosis			
No	366 (68.4%)	121 (71.2%)	
Yes	169 (31.6%)	49 (28.8%)	0.497[C]
HIV			
No	465 (86.9%)	154 (90.6%)	
Yes	70 (13.1%)	16 (9.4%)	0.202[C]
P= Z-test of two proportions, C=Chi squared test, W=Wilcoxon rank sum test			

Table 2: Comparison of the BIC between Parametric Models		
Model	**Number of Parameters**	**BIC**
ExQonential	12	1646.709
Weibull	13	1269.99
	13	1480.346
Log-Normal	13	1157.343
Log-Logistic	13	1131.675
Generalised Gamma	14	1159.769

Table 3: Crude and Adjusted Time Ratios of the COVID-19 patients using the Log Logistic Model				
Factors	**Crude**	**p-value**	**Adjusted**	**p-value**
Age, years	**Time Ratio (95% CI)** 1.005 (1.002, 1.007)	0.001	**Time Ratio (95%CI)** 1.004 (1.002, 1.007)	0.001
Gender				
Female	Ref (1)		Ref (1)	
Male	0.993 (0.9167, 1.0757)	0.861	0.998 (0.924, 1.086)	0.969
Fever				
No	Ref (1)		Ref (1)	
Yes	1.062 (0.9714, 1.162)	0.187	1.029 (0.942, 1.125)	0.522
Cough				
No	Ref (1)		Ref (1)	
Yes	1.009 (0.940, 1.083)	0.899	0.993 (0.923, 2.366)	0.861
Sore throat				
No	Ref (1)		Ref (1)	
Yes	1.062 (0.981, 1.149)	0.138	1.058 (0.977, 1.178)	0.164
Dyspnoea				
No	Ref (1)		Ref (1)	
Yes	1.135 (1.041, 1.240,)	0.004	1.114 (1.018, 1.221)	0.019
Headache				
No	Ref (1)	Ref	Ref (1)	
Yes	0.995 (0.925, 1.070)	0.899	0.982 (0.911, 1.058)	0.635
Chest pain				
No	Ref (1)		Ref (1)	
Yes	1.060 (0.981, 1.145)	0. 139	1.051 (0.970, 1.138)	0.220
Vomiting				
No	Ref (1)		Ref (1)	
Yes	0.990 (0.904, 1.085)	0.832	0.960 (0.874, 1.473)	0.387
Tuberculosis				
No	Ref (1)		Ref (1)	
Yes	0.998 (0.926, 1.077)	0.961	0.996 (0.923, 2.529)	0.928
HIV				
No	Ref (1)		Ref (1)	
Yes	1.057 (0.949, 1.175)	0.258	1.043 (0.933, 1.579)	0.457

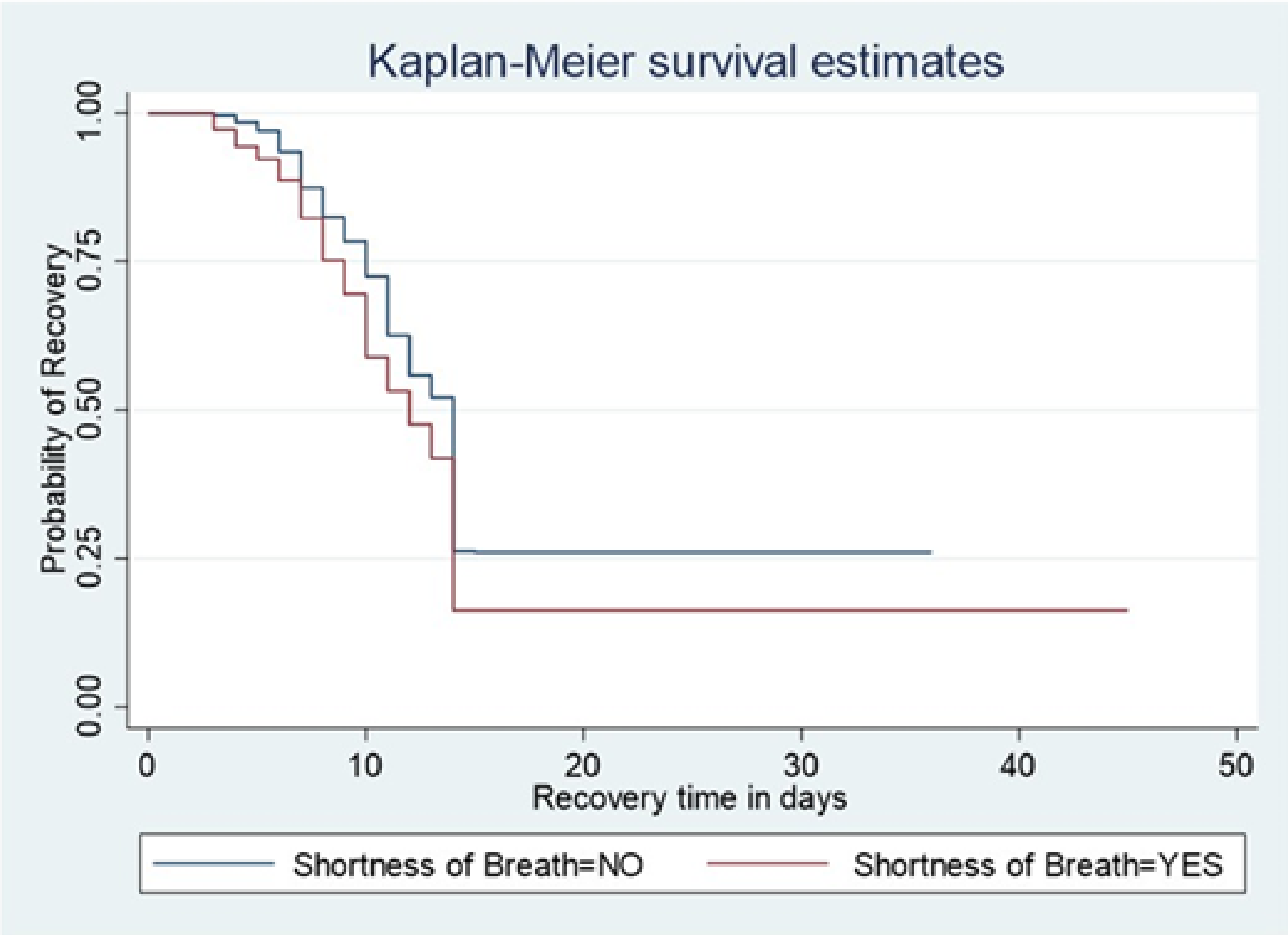

Figure 1: Estimates of the recovery time in days of COVID-19 patients

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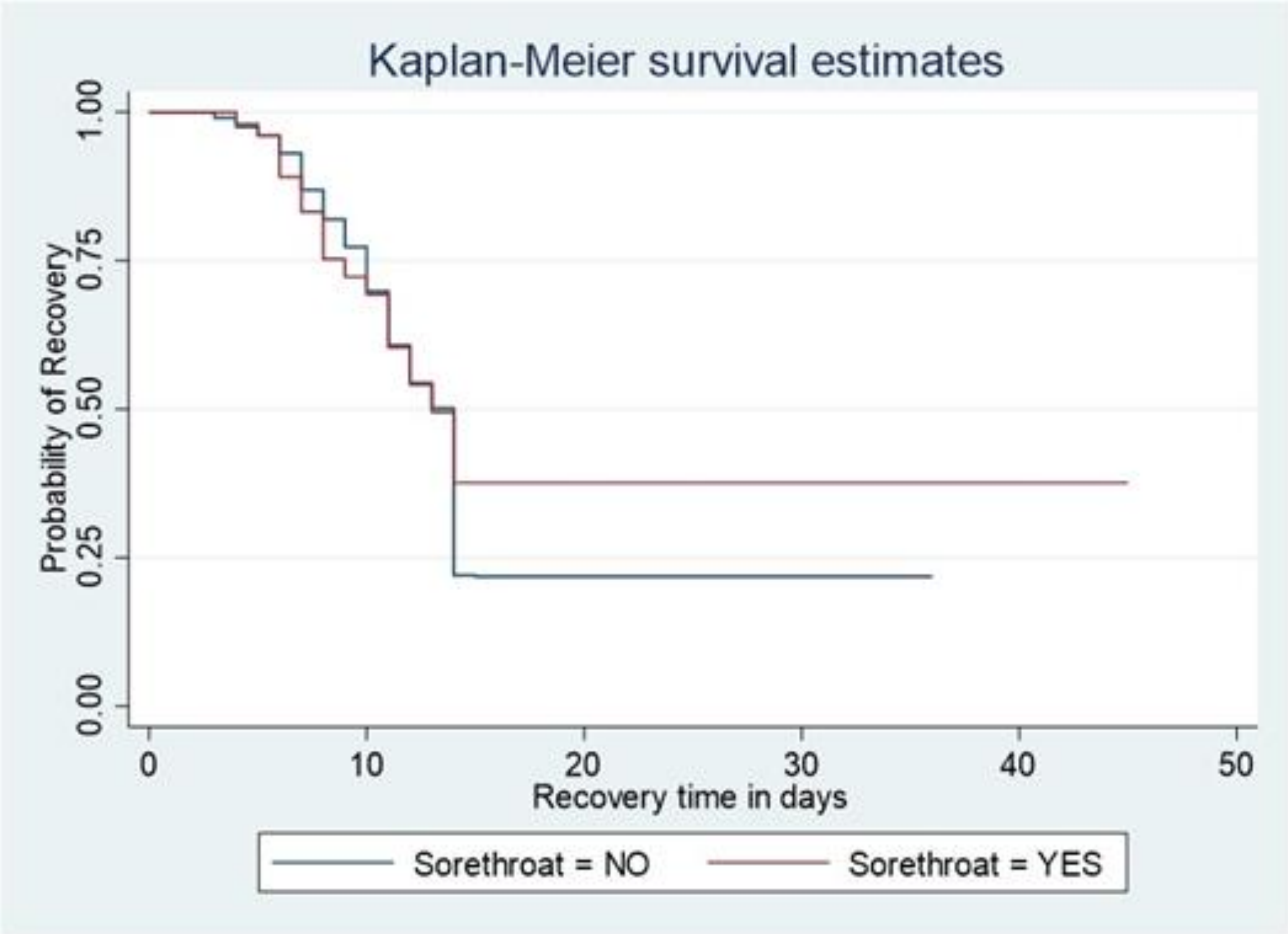

Figure 2: Estimates of the recovery time in days of COVID-19 patients

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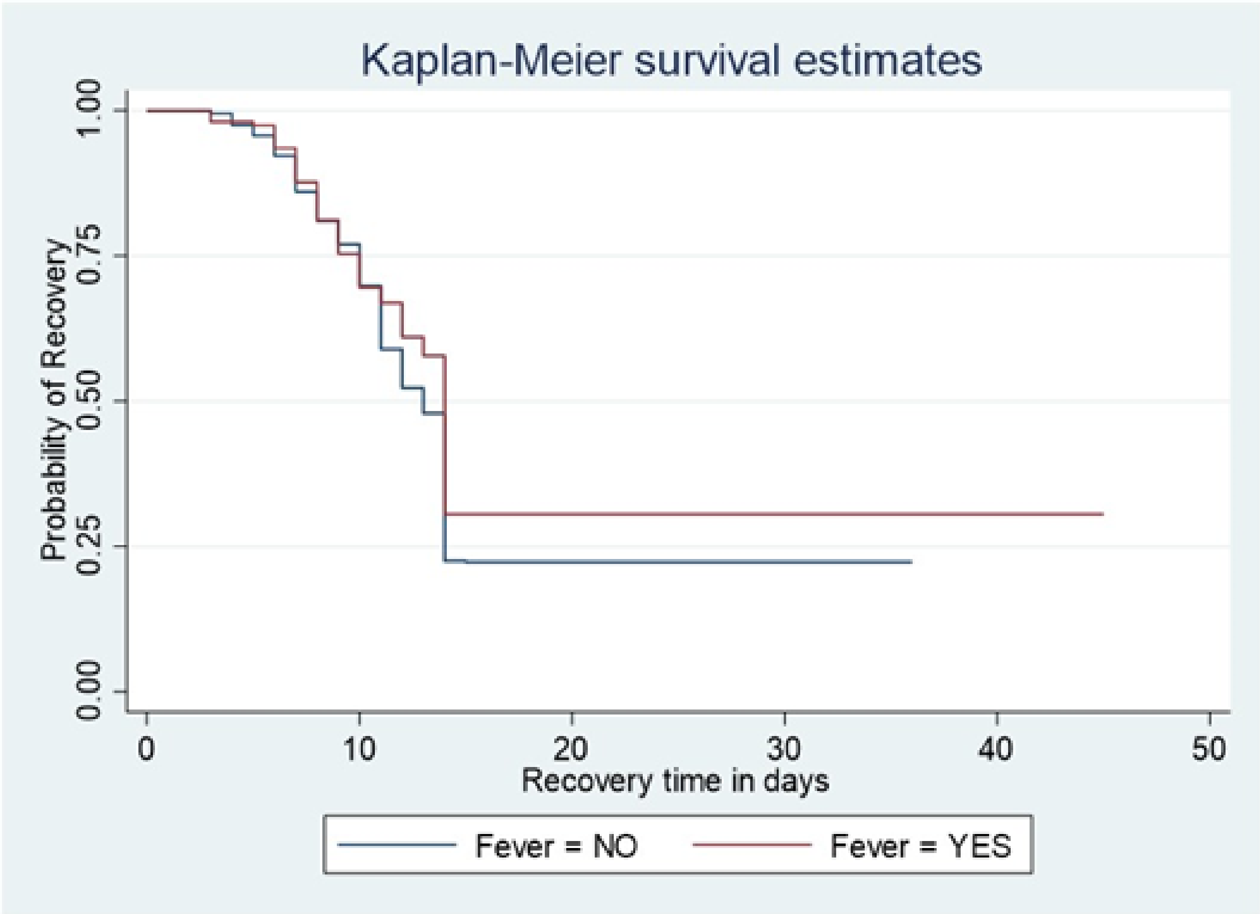

Figure 3: Estimates of the recovery time in days of COVID-19 patients

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