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Determinants of Covid-19 Recovery Time among Patients Hospitalized to Treatment Center in North-Central Ethiopia

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Abstract

Novel coronavirus disease 2019 (Covid-19), caused by the causative agent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become the consequential global health crisis and is one of the world leading causes of death. The current study was conducted to determine factors that affect time to recover from Covid-19 infection among patients hospitalized to the treatment center in North-Central Ethiopia. From May 9, 2020 to February 13, 2021, 352 patients suffering from Covid-19 infection and admitted to Boru Meda hospital Covid-19 treatment center were studied retrospectively. A Cox regression was used to analyze the socio-demographic and clinical factors that affect the recovery time. In the sample, about 30 percent of the patients recovered during the follow-up period, and the median time to recover was 19 days with a 95 percent confidence interval [17-21]. In addition, the recovery rate of patients with pre-existing conditions (HR=0.578; 95% CI: 0.370, 0.903), of patients aged 20-40 and above 40 (HR=0.567; 95% CI: 0.350, 0.919) and (HR=0.544; 95% CI: 0.301, 0.983), and patients receiving treatment (HR=0.626; 95% CI: 0.406, 0.936) were lower than their counterparts. In conclusion, the length of recovery from Covid-19 infection was delayed in patients with comorbidities, those who received treatment and those who were older.

Keywords: Cox regression, Covid-19, Boru Meda hospital, Ethiopia, Time to recover

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1. INTRODUCTION

Novel coronavirus disease 2019 (Covid-19), caused by the causative agent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China in 2019 and was initially associated with exposure to a seafood and live animal market [1]. Coronaviruses are respiratory viruses that are most commonly spread through the respiratory secretions of nearby infected people [2]. Most people who are infected with this virus will develop mild to moderate respiratory illness and recover without special treatment; however, some will become severely ill and need medical attention. Covid-19 has become the consequential global health crisis and is one of the world leading causes of death. As a result, on March 11, 2020, the World Health Organization (WHO) has declared the novel coronavirus outbreak as a public health threat and a global pandemic [3]. To date (June 15, 2023), it has been detected in 228 countries and territories, there have been more than 676 million confirmed cases, of which more than 6.8 million deaths reported worldwide [4] . Globally, USA is the country which highly affected by the disease as the number of confirmed cases and deaths is the highest in the world. Other countries with the highest number of confirmed cases and deaths include India, Brazil, France, the UK, Russia, and Germany [5]. Africa recorded its first case in Egypt in February 2020, and to date (June 15, 2023), there has been more than 12 million confirmed cases and more than 256 thousand deaths reported in Africa [6]. The number of cases and number of deaths of many African countries are low compared to European, American and Asian countries, this could be due to low test capacity, underreporting, and young population [7]. Several countries have implemented very strict restrictions to slow down the spread of Covid-19. These measures include closing schools, working from home, quarantine in areas with high numbers of cases, and most importantly, lockdown.

Instead of implementing a national lockdown like most governments, including those in Africa, Ethiopia introduced other essential measures in January 2020, far ahead of most developed countries. The first confirmed case of Covid-19 in Ethiopia was registered in Addis Ababa on the 13th of March 2020. Following this, the government intensified its response and implementing various multisectoral measures to counter its spread, including declaration of a national state of emergency on April 8, 2020[8]. Despite all those efforts of the

government and other stakeholders, the new cases are alarmingly increasing over the past year and a half. As of June 15, 2023, there have been 500,918 confirmed cases and 7,574 deaths reported to WHO which is one of the highest among African countries [5].

Covid-19 infection severity and mortality rates vary across different regions from corner to corner of the world, which can be attributed to differences in population characteristics. Several studies have indicated variation in recovery time following Covid-19 infection as well as factors associated with recovery time. The median recovery time from Covid-19 varies between patients and settings, such that some countries have more than 14 days and others have less than 14 days [9]. According to WHO, the recovery time is estimated to be 2 to 6 weeks [10]. The study in China reported the estimated median recovery time from Covid-19 of 13 days [11]. The estimated average time to recover from Covid-19 in Indian states/union territories ranges from 5 to 36 days [12], in Saudi Arabia was ranging from 15 to 11 days [13], and in Canada it was 22.4 [14]. The median recovery time of Covid-19 patients in Nigeria was 21 days [15]. From studies conducted in Ethiopia, the estimated median recovery time from Covid-19 in Kotebe was 19 days [16], in Bokoji was 13 days [17], in Wollega was 18 days [18], in Amhara regional state was 11 days [19]. Study results from different settings showed that recovery time from Covid-19 is affected by different factors. According to findings, factors like age [13], [18]–[20] sex [16], [17], presence of symptom [15], [16], [19] and comorbidity [16], [18], [19] have an association with recovery time from Covid-19. In light of the variation in recovery time among regions and factors that influence recovery time, localized research is necessary. This, along with the lack of research on the determinants of time to recover from Covid-19 infection in North-Central Ethiopia, prompted this study. Therefore, this study aimed to fill the existing gap about time to recover from Covid-19 infection by identifying factors that affect recovery time among patients infected with Covid-19 in North-Central Ethiopia.

2. METHOD

2.1. Study Setting, Design and Population

This study was conducted at Boru Meda Hospital Covid-19 treatment center which is the referral site of the Eastern Amhara region. The hospital is found in South Wollo zone, North-Central Ethiopia, with 100 beds, five mechanical ventilators, and two continuous positive airway pressure therapy machines. To identify Covid-19 patients, random testing was conducted on asymptomatic and symptomatic at-risk groups in public locations, such as bus stations, healthcare facilities, hotels, and banks. Additionally, the testing strategy targeted also targeted people from Covid-19 hot spots, contacts of confirmed cases, and clinically suspected cases, and all reverse transcription polymerase chain reaction (RT-PCR) SARS-CoV-2–positive cases in the region, regardless of severity, were admitted to the hospital [21] The study period was from the first day when the first case was admitted to the treatment center (May 9, 2020) to February 13, 2021. In this study a retrospective cohort study design was employed. All patients who were tested positive for Covid-19 by using the reverse transcription polymerase chain reaction (RT-PCR) test and admitted to Boru Meda Hospital Covid-19 treatment center from May 9, 2020 to February 13, 2021 were included in this study. The total number of Covid-19 patients admitted to the treatment center was 362. Since the medical record on some of the subjects was not complete this study utilized the data on 352 patients for whom complete information was obtained.

2.2. Data Collection

Important data about socio-demographic information and clinical data such as comorbidities, length of hospital stay, treatment provided and final clinical outcome were extracted from the patient medical records. To extract the data, we employed biostatisticians and public health professionals. The quality of the collected data was checked by the investigators.

2.3. Study Variables and Definitions

The outcome variable of the study was time to recover from Covid-19, that is, the length of time from the date of hospitalization to the date of discharge measured in number of days. The patients under treatment were discharged from the treatment center if they experience one of the following final clinical outcomes: after tested negative or cured, death, clinically improved or transferred to other treatment center. The patients were considered as event (uncensored) if they discharged after confirmed negative RT-PCR results, and, in contrast, patients were considered as censored if they died, clinically improved, or transferred to other treatment center. The predictor variables considered were: age, sex, comorbidity condition and treatment given. The variable treatment given is defined as the treatment given to support patients which includes unfractionated heparin (UFH) and dexamethason, ceftazidime and vancomycin. Note that this study is observational study and hence no subject was recruited in to clinical trial. The comorbidities identified in the sample are HIV, asthma, hypertension, diabetes mellitus, cancer, Viral respiratory illnesses (RVI) and respiratory syncytial virus (RSV).

2.4. Statistical Analysis

The data were entered using Epi-Info version 7.2.2.6 software and then the data cleaning, variable coding and statistical analysis were conducted using the statistical software STATA version 14.0 and R version 4.1.1. In this study we employed both descriptive and inferential statistical methods. The descriptive statistics we computed to summarize continues predictor variable(s) includes standard deviation and interquartile range (IQR). To summarize the survival time, we used the median which is a popular summary measure in survival analysis. This is due to the fact that the observed survival time has skewed distribution which results in outlying observation. Consequently, the median which is insensitive to outliers is an appropriate measure to summarize survival time. In addition, the 95 percent confidence interval estimate of the median is computed using the "log-log" approach that implemented in *survfit* function of the R *survival* package [22]. In order to summarize the distribution of categorical variables frequencies and proportions were used. The Kaplan-Meier survival curve [23] is one of the most frequently used non-parametric methods of time-to-event data analysis. The Kaplan-Meier method was used to describe the survival curves of categorical variables. The statistical significance of observed differences in survival curves of two or more groups of predictor variables was assessed using the log-rank test [24]. The Cox proportional hazards regression model, proposed by Cox [25], was used to identify determinant factors of time to recover from Covid-19. Although this approach is perhaps a gold standard in time to event data analysis, it relies on a strong assumption of proportional hazards across different predictor variables. Specifically, this model assumes that the hazards are proportional over time, which implies that each covariate has a multiplicative effect on the hazards function that is constant over time. If this assumption is violated, using the Cox model may lead to biased regression coefficient estimates and suboptimal significance tests, and consequently lead to misleading or erroneous conclusions. Therefore, a crucial step in fitting the Cox model is to check the proportional hazards assumption and take corrective measures if violated. To this end, a statistical test based on the Schoenfeld residual has become the standard approach for detecting violations of this assumption. Variables with a p-value less than or equal to 0.05 were considered as significantly associated with the Covid-19 recovery time.

3. RESULTS AND DISCUSSION

3.1. Socio-demographic and C linical Characteristics of Patients

The Covid-19 treatment center of Boru Meda Hospital had 362 patients admitted during the period from May 9, 2020 to February 13, 2021. Of these, 352 patients had complete medical records and were included in the final analysis. The socio-demographic and clinical characteristics distribution of the patients is presented in Table 1. Of the total 352 patients, 254(72.2%) were males and 98(27.8%) were females. The median age of the study subjects was about 29 years with IQR 23-43, and majority of the patients, 213(60.5%), were in the age group 20-40 and about one fourth of the patients were given treatments such as ceftazidime, dexamethasone and unfractionated heparin. Regarding pre-existing medical conditions, 71(20.2%) of the study participant had comorbidity. During the follow-up period from May 9, 2020 to February 13, 2021, 218 out of a total of 352 patients were event-free (censored), and 134 of them experienced the event of interest (recovered). The percentage of subjects who experienced the event of interest (recovered) was found to be high for the age group < 20 years (48.8%) than age groups 20-40 (39.0%) and > 40 (31.2%). About 35.8% and 43.9 % of male and female patients recovered from Covid-19. Among patients with (without) pre-existing medical condition about 36.6% (38.4%) recovered. The recovery rates for patients who received treatments and who did not received treatments were 33% and 39.9%, respectively.

Table 1. Distribution of socio-demographic and clinical characteristics of patients hospitalized to the treatment center in North-Central Ethiopia, from May 9, 2020 to February 13, 2021

Predictor variables	Categories	Recovery status		Total
		Recovered (%)	Censored (%)	N (%)
Sex	Male	91(35.8)	163(64.2)	254(72.2)
	Female	43(43.9)	55(56.1)	98(27.8)
Age	< 20	21(48.8)	22(51.2)	43(12.2)
	20-40	83(39.0)	130(61.0)	213(60.5)
	> 40	30(31.2)	66(68.8)	96(27.3)
Comorbidity	Yes	26(36.6)	45(63.4)	71(20.2)
	No	108(38.4)	173(61.6)	281(79.8)
Treatment given	Yes	31(33.0)	63(67.0)	94(26.7)
	No	103(39.9)	155(60.1)	258(73.3)

3.2. Time to Recover from Covid-19

In this study we used the Kaplan-Meier survival curve and the median survival time to summarize the difference in time to recover from Covid-19 of categories of predictor variables. The median time to recover from Covid-19 infection was estimated to be 19 days with 95% CI [17, 21]. The estimated Kaplan-Meier functions for the groups of categorical variables are presented in Figure 1. From the plot, there were no clearly noticeable differences in the chance to recover from Covid-19 among male and female patients. This is also revealed from the estimated median recovery time and the result of the log-rank test (Table 2 and Figure 1). In contrast, as indicated in the estimated median recovery time and the estimated survival curves, there were differences among patients with and without pre-existing medical conditions. There was also a significant difference in duration to recover for the predictor variables age and treatment given. Patients with pre-existing medical condition, with age greater than forty, and those who received treatment takes longer time to recover from Covid-19 as compared to their counterparts (Table 2). The results of the log-rang test presented in Table 2 revealed that there were significant differences among patients infected with Covid-19 in relation to the predictor variables age, comorbidity and treatment given.

3.3. Results of the Cox Proportional Hazards Regression Analysis

In this study, the determinant factors were identified by analyzing the Cox proportional hazards regression model. In this study, we checked proportional hazards assumption for each predictor variables (i.e. Age, Sex, Comorbidity and Treatment given) and global test using the Schoenfeld residual based test implemented in the R function *cox.zph* of *survival* package and the results are given in Table 3. From this table, all the four predictor variables did not violate the Cox proportional hazards assumption as the p-values are greater than the level of significance. Hence, in our final model we considered all the predictor variables.

The results of the fitted Cox proportional hazards regression analysis presented in Table 4 showed that age, comorbidity and treatment given are significant factors that influence the time to recover from Covid-19. The estimated hazard ratio (HR) for patients with pre-existing medical conditions was found to be 0.578 (95%CI: 0.370, 0.903) meaning that the recovery rate of patients with comorbidity was about 42% lower than patients who had not admitted with comorbidity. The confidence interval indicated that the recovery rate for patients with pre-existing medical condition could be as low as 10% and as high as 63%. Patients in the age groups 20-40 and > 40 had 43.3% (HR = 0.567; 95%CI: 0.350, 0.919) and 45.6% (HR = 0.544; 95%CI: 0.301, 0.983) lower chance to recover from Covid-19, respectively, compared to patients in the reference age group (< 20) controlling for all the other variables in the model. Similarly, patients who received treatment had about 37% (HR = 0.626; 95%CI: 0.406, 0.936) less likely to recover earlier compared to their counterparts.

Table 2. Estimated median recovery time and results of the log-rank test for sociodemographic and clinical characteristics of patients hospitalized to the treatment center in North-Central Ethiopia, from May 9, 2020 to February 13, 2021

Predictor variables	Category	Median[95%CI]	Log-rank Chi-square	df	p-value
Sex	Male Female	18[16, 21] 20[16, 23]	0.53	1	0.465
Age	<20 20-40 >40	15[13, 21] 17[16, 21] 21[18, 22]	8.85	2	0.012
Comorbidity	Yes No	21[17, 38] 18[16, 21]	7.49	1	0.006
Treatment given	Yes No	21[18, 30] 17[16, 21]	6.09	1	0.014

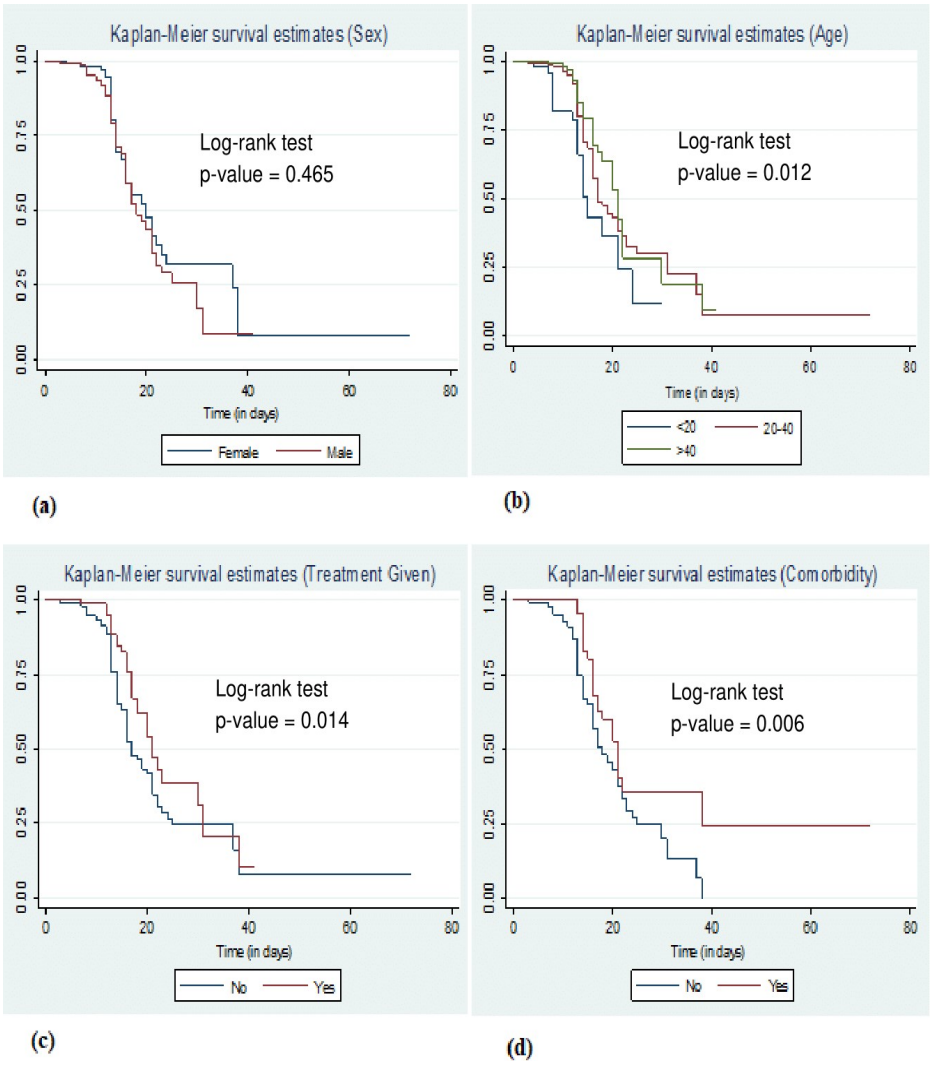

Figure 1. Estimated Kaplan-Meier plots of recovery time of patients hospitalized to the treatment center in North-Central Ethiopia for the variables: sex(a), age(b), comorbidity(c) and treatment given(d).

Table 3. Results of the proportional hazard assumption for variables age, sex, comorbidity and treatment given and global test using Schoenfeld residuals-based test

Predictor variables	Chi-square	df	p-value
Sex	2.490	1	0.11
Age	0.263	2	0.61
Comorbidity	0.370	1	0.54
Treatment given	1.592	1	0.45
Global test	3.873	5	0.57

Table 4. Results of the Cox regression analysis of time to recover from Covid-19 among patients hospitalized to the treatment center in North-Central Ethiopia, from May 9, 2020 to February 13, 2021

Predictor variables	Category	Parameter Estimate	s.e.	z	p-value	Estimated HR	95% CI Lower	for HR Upper
Sex	Male	0.171	0.193	0.890	0.374	1.187	0.814	1.730
	Female					1		
Age	<20					1		
	20-40	-0.567	0.246	-2.300	0.021*	0.567	0.350	0.919
	>40	-0.608	0.302	-2.020	0.044*	0.544	0.301	0.983
Comorbidity	Yes	-0.548	0.228	-2.410	0.016*	0.578	0.370	0.903
	No					1		
Given treatment	Yes	-0.469	0.220	-2.130	0.033*	0.626	0.406	0.963
	No					1		

3.4. Discussion

The aim of this study was to determine time to recover from Covid-19 infection and its association with socio-demographic and clinical variables among patients hospitalized to the treatment center in North-Central Ethiopia. To this end, the current study used 352 patients who followed retrospectively from May 9, 2020 to February 13, 2021. To highlight a key result, the median time to recover from Covid-19 infection was found to be 19 days with 95% CI [17, 21]. This finding was consistent with other institution- based studies in Eka Kotebe General Hospital, Ethiopia indicated 19 days [16], Wollega University referral hospital, Ethiopia reported 18 days [18], and Jingyintan Hospital and Wuhan Pulmonary Hospital, China indicated 20 days [26]. Moreover, similar numbers also reported from studies conducted in Shenzhen, China 21 days [27] and in Israel ranges from 20 to 21 days [28]. In contrast, there are many studies that indicated lower median time to recover from Covid-19 infection. These includes the study conducted in Boru Meda hospital, Ethiopia, 13 days [21], Bokoji hospital, Ethiopia, 13 days [17], Guangzhou Eighth People's hospital, China, 12 days [29], Al-Noor specialist hospital in Mecca, Saudi Arabia, 6 days [13] and Aga Khan University hospital, Pakistan, 6 days [30]. The possible explanation for the variation in median number of days to recover from Covid-19 infection between studies might be attributed to the differences in length of follow-up period, sample size, study setting, socio-demographic and clinical characteristics, and disease severity.

In this study, the association between time to recover from Covid-19 and predictor variables was also assessed using the Cox regression analysis. From this, the factors: age, comorbidity and treatment given came out as significant predictors associated with recovery time of Covid-19 infection whereas sex was found to be a non-significant factor. The results of this study showed that patients with pre-existing medical condition had about 42% lower rate to recover from Covid-19 as compared to those without pre-existing medical condition. The study conducted in Eka Kotebe General Hospital, Ethiopia [16], Wollega University referral hospital, Ethiopia [18], Boru Meda hospital, Ethiopia [21], Wuhan Pulmonary Hospital, China [31], Tianyou Hospital, China [32] and Al-Noor specialist hospital in Mecca, Saudi Arabia [13] are some of the existing evidences that support the finding of this study. The lower recovery rate of patients with comorbidity might be due to the fact that it may worsen the immune status and there may be differences due to the nature of treatment for comorbidities. Furthermore, the factor treatment given was also significantly associated with time to recover form Covid-19. The recovery rate of patients who received treatment was about 37% lower than those who did not received treatment. This is consistent with the finding in Ethiopia [17] and China [32] that found patients under treatment were associated with delayed recovery time. This might be due to the fact that patients who receive treatment were those with moderate or severe Covid-19 status. Moreover, patients aged 20 to 40 and above 40 years had about 43% and 56% lower recovery rate as compared to those aged below 20 years. This evidence was supported by studies conducted in Ethiopia [21], Kenya [33], China [20], [29], [31], [34], and Saudi Arabia [13]. The possible explanations of this might be the T-cell diversity alterations, inflammaging and immunosenescence that the immune system undergoes with aging. Finally, sex had no significant association with time to recover from Covid-19. This is in line with the finding conducted in in Ethiopia [21], Kenya [33], China [20], [29], [31], [34] and Saudi Arabia [13]. Contrary to these studies, other authors reported sex as significant predictor of recovery time [16], [17].

This study is noteworthy for using an advanced statistical technique to account for the censored nature of the data. Moreover, giving treatments for the patients were examined in this study in order to determine the extent to which they affect the recovery time. For medical practitioners and policymakers, this is crucial to make

informed decisions. In spite of these strengths, this study also has the limitation that there may be very important variables missing from medical records that could affect recovery times from Covid-19 infections.

4. CONCLUSION

The aim of this study was to determine factors that affect recovery time of patients infected with Covid-19. Time to recover from Covid-19 was significantly associated with factors; age, comorbidity and treatment given. Furthermore, patients with comorbidity, received treatment and older age were associated with delayed duration of recovery from Covid-19 infection. Consequently, healthcare providers should give priority to patients with pre-existing medical condition, elders and those who received treatment.

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