

ORIGINAL RESEARCH

Clinical Features and Time to Recovery of Admitted COVID-19 Cases at Dilla University Referral Hospital Treatment Center, South Ethiopia

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Background: Since coronavirus disease 2019 emergence, millions were infected and many were dying because of the virus. Clinical features and time to recovery of admitted clients vary across settings. Therefore showing clinical features and recovery time from COVID-19 in a different setting is necessary to design appropriate treatment and preventive measures. So, this study attempted to investigate the clinical features and time to recovery of admitted clients to Dilla University Referral Hospital treatment center,

Methods: A retrospective study design was conducted in 220 patients confirmed by real time polymerase chain reaction and admitted to Dilla University Referral Hospital treatment center from September 2020 to July 2021. Data were collected from the patients' record. Data entry was done by an Epi-Info version 7.2.1.0 and analyzed by Statistical Package for the Social Sciences version 25 software. Descriptive statistics were used for clinical features, and median time to recovery was computed by using Kaplan-Meier. Results: Common clinical features were cough 209 (95%), shortness of breath 153 (69.5%), fever 133 (60.5%), headache 75 (34.1%), easy fatigue 68 (30.9%), joint pain 56 (25.5%), tachypnea 197 (89.5%), hypoxia 95 (43.2%), and tachycardia 83 (37.7%). The overall median recovery time for admitted cases was 5 days. There was significant difference between recovery probability of severe and moderate cases, severe and mild cases (p=0.00), who had normal body temperature and hypothermic (p=0.05), who had normal breathing rate and bradypnea patients (p= 0.014).

Conclusion: COVID-19 patients frequently show cough, shortness of breath, fever, headache, easy fatigue and joint pain. Median time to recovery was 5 days. Having a normal body temperature, normal breathing rate, and severe disease status had statistically significant association with median recovery time. So, close follow up is required for client admitted with severe disease.

Keywords: COVID-19, clinical features, time to recover

Introduction

Coronaviruses are enveloped RNA viruses that infect humans and other animals. They were first described in 1966 by Tyrell and Bynoe. The virus changes over time and some changes may affect the virus properties. Due to this change, different sub-families of the virus are emerging: alpha (B.1.1.7), beta (B.1.351), gamma (P.1) and delta (B.1.617.2) exist. Alpha and beta-coronaviruses originate from mammals, in specific from bats, while gamma and delta are from pigs and birds.^{3,4} Beside four variants, on November 24, 2021 the B.1.1.529 commonly called an Omicron variant of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that contains a high number of mutations was also detected.⁵ These variants are now designated by the World Health Organization (WHO) as SARS-CoV-2 variants of concern.⁶ There are also other variants named variants of interest, that include Epsilon variant, Zeta variant, Eta variant, Theta variant, Iota variant and Kappa variant. The virus spread from human to human by droplets and contact routes, but some uncertainty about airborne, there is also fecal or intrauterine transmission. 8 Various SARS-CoV-2 variants are detected

since the first covid-19 cases emerged in Wuhan, like that detected in United Kingdom (UK), South Africa, Brazil. 9,10 The emerging variants appear to be more communicable than the wild-type SARS-CoV-2 that contains mutations in the spike protein, urging vaccine efficacy concerns. 11 Although some studies indicated no significant differences between the case fatality ratio of Delta and non-Delta variants, 12 but still not much is known about these variants. 13 The vaccine efficacy could be influenced by the emergence of new SARS-CoV-2 variants with a major antigenic drift. Some recent reports indicated that the harmful effect of RNA binding motive (RBM) mutations on the neutralization activity of vaccine-elicited antibodies. 14

Forty percent of people with COVID-19 develop only mild or moderate disease, while approximately 15% develop severe disease and 5% develop critical disease complications like respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic. ¹⁵ Most of them show fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgia (11–35%), ¹⁶ other non-specific symptom like a sore throat, nasal congestion, headache, diarrhea, nausea and vomiting. ¹⁷

Age more than 60 years, underlying co-morbidities like diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immunosuppression and cancer have been associated with higher death and time to recovery. The recovery time varies from person to person and affected by the severity of the disease. Its case fatality rate was 6.3%, but it is different in different ages and countries. It shows the very strong risk stratification across age, socioeconomic factors, and clinical factors. Long-term social isolation due to the COVID-19 infection sometimes leads to depression and post-traumatic stress.

SARS-CoV-2 has now spread to many other countries,²⁹ as a result Artificial Intelligence-driven tools should be implemented as cross-population train (test) model.³⁰ The collective number of cases reported worldwide is now nearly 216 million and the collective number of deaths is just 4.5 million.³¹ Over 2.7 million new cases were reported globally, the Americas and Europe account for about 80% of new cases and new deaths reported worldwide, while it shows 10% prevalence in Africa.³² There have been more than three hundred thousand confirmed cases of COVID-19 with more than five thousand deaths in Ethiopia.³³ The surge is increasing on international and local levels, causing rapid loss of life, joblessness, the decline of the healthcare systems, and both local and international economies.³⁴ Susceptibility to COVID-19 infection seems high across Ethiopia, mainly in Somali, Afar, Amhara, Oromia and Tigray regions.³⁵ The number of severe cases requiring admission to the Hospital and intensive care unit is high across Amhara, most parts of Oromia and some parts of the Southern Nations, Nationalities and Peoples' Region.³⁶ The risk of COVID-19-related death is also high in the country's border regions, where public health readiness is limited.^{35,37}

The virus entry into human cell is mediated by the trimeric viral Spike glycol-protein that contains the exterior S1 and trans-membrane S2 subunits. The Spike is the main target of the cellular and humoral immune responses against SARSCoV-2 upon natural infection.^{9,38} Long lasting immune protection involves antibodies that recognize the viruses and neutralize them; different types of T cells that kill the pathogen.³⁹ Even though all immune components have been found in people who recover from this virus, sufficient information about immune response and how long it lasts after infection is unknown.⁴⁰ Most importantly, reports of reinfection with the virus have raised concerns that the immune response to it might not be durable.^{41,42} The appearance of new variants with the different capacity to evade polyclonal antibody responses could possibly lead to a rising number of reinfections.^{9,43,44} Preventive measures for COVID-19 that include vaccination, wearing masks and social distancing are vital mainly for older or those who have several or severe health conditions. Some scientific research has been done in many features of COVID-19, but still need localized valid and reliable information is needed in order to intervene properly. Different studies have shown different median recovery time of COVID-19 admitted patients and it varies across disease status.⁴⁵ So, this study attempted to describe baseline clinical features and time to recovery of COVID-19 cases admitted to Dilla University Referral Hospital treatment center.¹⁹

Methods and Materials

Operational Definitions

Time to recovery is the time when the patients were diagnosed positive for COVID19 to the time when the patients diagnosed negative by RT-PCR by two consecutive tests and being free of symptoms after admission to the Hospital. The

event was recovery from the disease, while censored were the patients who were not developed an event; those who died or transferred out during the study period. Mild cases were symptomatic patients without evidence of viral pneumonia or hypoxia, moderate were the cases with clinical signs of non-severe pneumonia while severe cases were the cases with clinical signs of severe pneumonia like fever, cough, dyspnea and respiratory rate >30 breaths/minute or SPO2 <90%.

Data Collection

This study was conducted at the Dilla University Referral Hospital, South Ethiopia. A retrospective study design was used for all 220 COVID-19 confirmed patients by RT-PCR; who were admitted to Dilla University Referral Hospital treatment center from September 2020 to July 2021. All data related to socio-demographic information, clinical features and co-morbidities were collected from the patients' record. General practitioners and Nurses who were working at treatment center were trained and then collected the data from the patients' record.

Data Analysis

Data entry was done by an Epi-Info version 7.2.1.0 and analysis was done by Statistical Package for the Social Sciences (SPSS) version 25 software. Descriptive statistics were used for socio-demographic factors and clinical features, and median time to recovery was done by using Kaplan-Meier method. The cox regression analysis was used to determine factors associated with time to recovery for hospitalized COVVID-19 patients.

Ethical Approval

Ethical approval and waiver consent was obtained from the Institutional Review Board (IRB) of the Dilla University College of Medicine and Health sciences under the protocol unique number of duirb/002/21-10 before the data collection. The consent to participate in the study was not applicable because the study was retrospective and was conducted on the data collected from the patients' medical records. Therefore, it was difficult to obtain consent from already discharged patients from the Hospital. However, the privacy and confidentiality of their personal information were protected according to ethical principles for medical research involving human subjects of the World Medical Association Declaration of Helsinki.

Results

Socio-Demographic Factors

Out of 220 study cases, 113 (51.4%) of them were above 50 years of age, and the mean age was 47 years. Most of the cases 123 (55.9%) were male, and house wife accounted for the largest number of cases 47 (21.4%) followed by unemployment 41 (18.6%), Government employees 31 (14.1%), farmers 30 (13.6%), self-employed 28 (12.7%), merchants 20 (9.1%) and students (6.8%) (Table 1).

Clinical Features and Co-Morbidity with Chronic Diseases

The most common clinical symptoms were cough 209 (95%), shortness of breath 153 (69.5%), fever 133 (60.5%), headache 75 (34.1%), easy fatigue 68 (30.9%) and joint pain 56 (25.5%). Most cases had tachypnea 197 (89.5%), while the others had hypoxia 95 (43.2%), tachycardia 83 (37.7%), and hypertension 36 (16.4%). Of all cases, 120 (54.5%) were severe, 89 (40.5%) were moderate and 11 (5.0%) were mild.

Among 133 (60.5%) cases that had chronic diseases, 27.3% were hypertensive, 20.9% had type II Diabetes Mellitus, 14.5% had Tuberculosis, 6.8% had Cardiac disease, 4.1% had renal disease, 2.3% were Asthmatic patients, 1.8% had (Human Immuno-Virus) HIV, 0.9% had type I Diabetes Mellitus, and 0.9% had chronic liver disease, 0.5% had prostate cancer, advanced cervical cancer, chronic lymphocytic leukemia, severe Diabetes keto-acidosis (DKA) respectively.

Of the 220 study cases, 167 (75.9%) cases were improved while 49 (22.3%) of them were died. Twenty nine (59.2%) of died cases were beyond the age of 50+ years while 11 (22.4%) were between the age group of 30–49 years and 9 (18.4%) were <30 years. Out of 220 admitted COVID-19 cases, 49 reported died, and of them, males accounted for 28 (57.1%) while the females were 21 (42.9%). Likewise, 31 (63.3%) had fever, 2 (4.1%) were hypothermic, 27 (55.1%)

Table I Socio-Demographic Factors of Hospitalized COVID-19 Patients (n=220) to Dilla University Referral Hospital, December 2021

Socio-Demographic Factors		Frequency	Percent
Sex			
	Male	123	55.9
	Female	97	44.1
Age			
	<30 years	38	17.3
	30-49 years	69	31.4
	50+ years	113	51.4
Occupation			
	House wife	47	21.4
	Unemployed	41	18.6
	Government employed	31	14.1
	Farmer	30	13.6
	Self-employed	28	12.7
	Merchant	20	9.1
	Student	15	6.8
	Daily laborer	4	1.8
	Driver	3	1.4

were tachycardia, 1 (2.0%) were bradycardic, 45 (91.8%) were tachypnea, 2 (4.1%) were bradypnea, 9 (19.1%) were hypertensive, 6 (12.8%) were hypotensive. Of the 32 (65.3%) that had a chronic disease, type II Diabetes mellitus (DM) accounted 10 (20.4%) and the others had cardiac disease 3 (6.1%), renal disease 1 (2.0%), Tuberculosis 7(14.3%), type 1 DM 2(4.1%), HIV 1 (2.0%), chronic lymphocytic leukemia 1 (2.0%). Most of the COVID-19 died cases that had comorbidity with chronic diseases were severe 48 (98.0%), and the moderate 1 (2%) while 37 (75.5%) were with hypoxia.

Among 165 improved cases, 80 (48.5%) were beyond the age group of 50 years while 57 (34.5%) were between 30–49 and 28 (17.0%) were <30 years, and 96 (58.2%) were male. Of them, 101 (61.2%) had fever and 54 (32.7%) were tachycardia, 148 (89.7%) were tachypnea, 26 (16.3%) were hypertensive, 99 (60.0%) had chronic diseases: 12 (7.3%) had cardiac disease, 7 (4.2%) had renal disease, 25 (15.2%) had Tuberculosis, 35 (21.2%) had type II DM. 55 (33.3%) hypoxia, 70 (42.4%) were severe, 85 (51.5%) were moderate and 10 (6.1%) were mild cases (Table 2). The mean length of stay at Hospital was 5.65 (range, 1 to 30) days while it was 5.55 (range, 1 to 25) days for improved cases and 6.06 (1 to 30) days for died cases. Furthermore, the severe cases stay longer at Hospital than mild cases (AHR=0.356, p=0.002).

Time to Recovery of COVID-19 Cases

The overall median recovery time for admitted COVID-19 patients was 5 days. It was 8 days for severe cases, 4 days for moderate and mild cases. The Kaplan-Meier and Log rank test showed that there was a significant difference between recovery probability of severe and moderate cases, severe and mild cases (p=0.00). However, there was no significant difference between the recovery probability of moderate and mild cases (p=0.91), (Figure 1).

The median recovery time for the COVID-19 patients that had co-morbidity with chronic diseases was 6 days while it was 5 days for cases that had no chronic diseases. Furthermore, the Kaplan-Meier and Log rank test showed a statistically significant recovery probability difference between these cases (p=0.015), (Figure 2). The median recovery time for female and male was 6 and 5 days respectively, with the overall 6 days median time. There was no statistically significant recovery probability difference between male and female (p=0.34), (Figure 3). The median recovery time for <30, 30–49 and 50+ year age groups was 5, 5, and 7 days respectively. On the other hand, there was statistically significant recovery probability difference between the age group of above 50 and 30–49 years (p= 0.01), while no significant difference observed with the other age group (p=0.69), (Figure 4).

Table 2 Clinical Features of Hospitalized COVID-19 Patients (n=220) to Dilla University Referral Hospital, December 2021

Clinical Features		Frequency	Percent
Symptoms	Cough	209	95.0
	Fever	133	60.5
	Shortness of breath	153	69.5
	Sore throat	8	3.6
	Loss of test	29	13.2
	Loss of smell	31	14.1
	Headache	75	34.1
	Easy fatigue	68	30.9
	Joint pain	56	25.5
	Chest pain	13	5.9
	Loss of appetite	19	8.6
Body temperature	Fever	133	60.5
	Hypothermia	15	6.8
Pulse rate	Tachycardia	83	37.7
	Bradycardia	2	0.9
Breathing rate	Tachypnea	197	89.5
	Bradypnea	5	2.3
Blood pressure	Hypertensive	36	16.4
	Hypotensive	21	9.5
Oxygen saturation	Нурохіа	95	43.2
Disease status	Severe	120	54.5
	Moderate	89	40.5
	Mild	П	5.0

Factors Associated with Recovery Time of COVID-19 Cases

In bivariate co-regression analysis, factors like oxygen saturation, temperature, breathing rate, cough, easy fatigue, joint pain, co-morbidity with chronic disease, disease status showed a statistical association with median recovery time. However, by adjusting for confounders in multivariate cox-regression analysis, only having normal body temperature, breathing rate (normal), disease status (severe) remained statistically significant (AHR=0.52, 95% CI= 0.25–1.00, P=0.05), (AHR=5.37, 95% CI=1.40–20.57, p=0.014), and (AHR=0.33, 95% CI=0.16–0.6, P=0.002) respectively. That means that the patients who had a normal body temperature were 48% less recovery time as compared to those hypothermic clients. Furthermore, the patients who were detected with normal breathing rate had shorter recovery time than patients who showed bradypnea on admission time. Severe patients had longer recovery time as compared to those patients who had admitted with mild status (Table 3).

Discussion

This study included all the 220 COVID-19 cases that were admitted to Dilla University Referral Hospital Covid-19 treatment center. The majority of the study cases were male (55.9%) and most of the study cases were above 50 years, and the mean age was 47 years. COVID-19 infected patients frequently show clinical symptoms like fever, cough, myalgia and shortness of breath and sore throat, 46,47 and some may do not experience any symptom. Similarly, our study indicated that the most common clinical symptoms were cough 209 (95%), shortness of breath 153 (69.5%), fever 133 (60.5%), headache (34.1%), easy fatigue (30.9%) and Joint pain (25.5%). This is high as compared to the study done in Kuyha COVID-19 Isolation and Treatment Centre, Mekelle University, North Ethiopia, where cough 354 (50.6%), myalgia 212 (31.1%), headache 196 (28.7%), fever 161 (23.6%) stated as the most frequently observed clinical symptoms. Most importantly, the majority of the patients were also shown tachypnea (89.5%) hypoxia (43.2%), tachycardia (37.7%). This finding is lower than the study done in Addis Ababa, Ethiopia, which stated that hypoxia

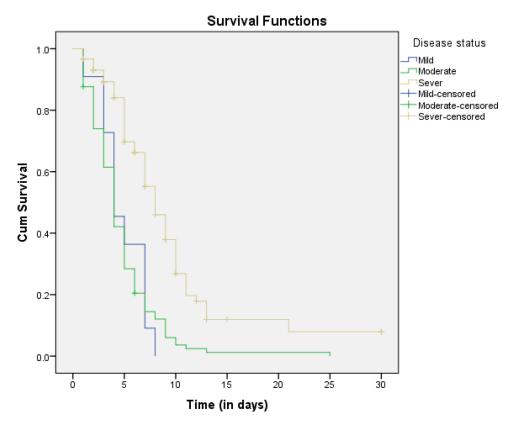


Figure I Recovery of COVID-19 patients admitted to the Dilla University Referral Hospital Treatment Center by disease status at admission.

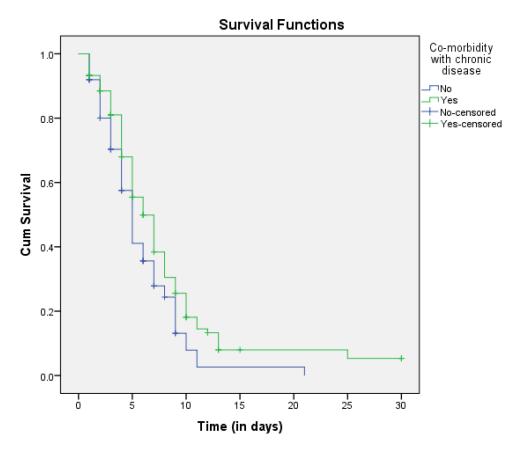


Figure 2 Recovery curve of COVID-19 patients admitted to the Dilla University Referral Hospital Treatment Center by co-morbidity with chronic diseases.

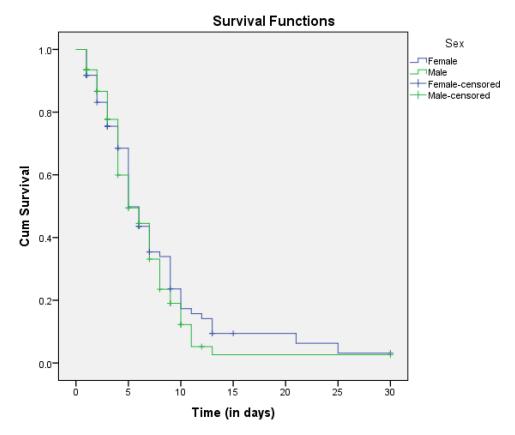


Figure 3 Recovery curve of COVID-19 patients admitted to the Dilla University Referral Hospital Treatment Center by sex.

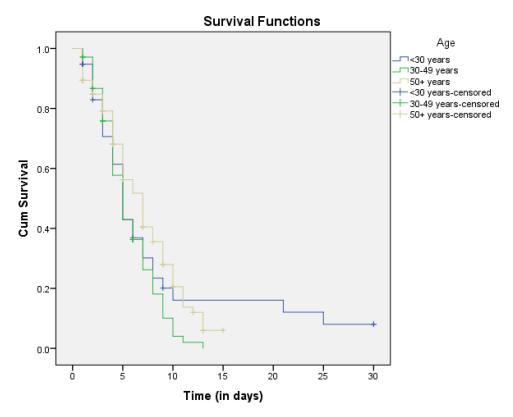


Figure 4 Recovery curve of COVID-19 patients admitted to the Dilla University Referral Hospital Treatment Center by age.

Table 3 Multivariate Cox-Regression Analysis Showing Adjusted Hazard Ratios of Clinical Features of COVID-19 Patients at Dilla University Referral Hospital, December 2021

Variables	Category	CHR (CI)	AHR (CI)	P value
Presence of cough	No	I	I	
	Yes	0.57 (0.29-1.07)	0.91 (0.43–1.91)	0.80
Presence of easy fatigue	No	1	1	
	Yes	0.73 (0.52-1.01)	1.08 (0.74–1.58)	0.69
Presence of joint pain	No	1	1	
	Yes	1.33 (0.95–1.86)	0.89 (0.75-1.06)	0.18
Body temperature	Hypothermia	1	1	
	Normal	0.38 (0.21–0.70)	0.52 (0.27-1.00)	0.05
	Fever	0.49 (0.28–0.89)	0.70 (0.37-1.34)	0.29
Presence of chronic disease	No	1	1	
	Yes	0.69 (0.50-0.95)	0.86 (0.61-1.20)	0.37
Severity of disease	Mild	1	1	
	Moderate	0.98 (0.52-1.84)	0.83 (0.43-1.59)	0.57
	Severe/Critical	0.36 (0.19–0.68)	0.33 (0.16–0.67)	0.002
Breathing rate	Bradypnea	1	1	
	Normal rate	4.28 (1.17–15.64)	5.37 (1.40–20.57)	0.014
	Tachypnea	2.79 (0.85–9.19)	3.36 (0.97-11.65)	0.056
Oxygen saturation	< 90	1	1	
	≥ 91	1.55 (1.12–2.14)	1.22 (0.84–1.75)	0.29

Abbreviations: CHR, crude hazard ratio; AHR, adjusted hazard ratio.

(60.5%) and tachycardia (52.9%),¹⁶ were the major clinical features; even though tachypnea (89.5%) was also shown common in our study. This is may be due to the sample size difference.

Our findings also indicated that the most common co-morbidities of the COVID-19 patients were hypertension (27.3%), type II Diabetes Mellitus (20.9%), Tuberculosis (14.5%), chronic heart disease (6.8%), renal disease (4.1%), Asthma (2.3%) and HIV (1.8%) which is higher than the other study done in Ethiopia that showed hypertension (1.6%), HIV (1.6%), diabetes (1.1%), and chronic respiratory diseases (1.1%) were the main co-morbidities noted;⁴⁸ but lower than the study that suggested COVID-19 admitted cases had hypertension (45%), DM (30%) and cardiovascular (20%) diseases,⁵⁰ and also different the that suggested the most common comorbidity was DM, followed by hypertension and HIV.¹⁶ This difference may be due to the sample size and age of the participants where most of current study cases were above 50 years.

On arrival to treatment center, most of the cases (79.2%) were severe to critical, while the rest (20.8%) were asymptomatic to mild. In our study, however, 54.5% were severe, 40.5% were moderate and 5.0% were mild. This means most of the cases were severe and moderate, which also differ from the study done at the Bokoji Hospital COVID-19 treatment center that stated most of the admitted covid-19 cases were severe (36.5%), asymptomatic (22.5%) and mild (21.6%). We also showed most of the cases (75.9%) were improved and 22.3% were died. Which is consistent with another study in Ethiopia that showed most of the admitted cases were improved (88.9%), while some of them died in the facility (11.1%). St

Our findings also stated that 49/220 cases were died and most of died cases (59.2%) were beyond the age of 50 years while 22.4% were between 30–49 years and 18.4% were <30 years. Furthermore, 57.1% of died cases were males. This is higher than the study in Brazil that suggested most deaths occurred in males (55.4%).⁵² This result is however, lower for males, but higher for females than the study done in Ethiopia that showed most deaths, 71% were males and 29% were females, ¹⁶ even though in both studies the number of died males were higher than females. This is may be due to Biological and sample size differences.

The overall median recovery time for treatment center admitted COVID-19 cases was 5 days. This is lower than the finding of the previous study that suggested the overall median recovery time of COVID-19 patients during treatment

was 24 days.⁵¹ This result is also different from result stated by the study done at the Wollega University Referral Hospital, which is 18 days.⁵³ This difference may be due to sample size, socio-demographic factors and severity of the disease. It was 8 days for severe cases, 4 days for moderate and mild cases. This indicates that it takes longer time to recover for severe cases than moderate and mild cases, which is consistent (in case of severe cases) with the previous study that stated the time needed for recovery was longer among patients with non mild disease (moderate and severe),⁵⁴ even though in our study both moderate and mild had the same median time. Furthermore, the severe cases stay longer at the treatment center than mild cases (AHR=0.356, p=0.002). There was statistically significant difference between recovery probability of severe and moderate cases, severe and mild cases (p=0.00). However, there was no significant difference between the recovery probability of moderate and mild cases (p=0.91).

Furthermore, the median recovery time for the Covid-19 patients that had co-morbidity with chronic diseases was 6 days while it was 5 days for cases that had no chronic diseases, and they have statistically significant recovery probability difference (p=0.015). This is different from the study done in Ethiopia at Millennium COVID-19 care center that stated the recovery time did not show statistically significant difference between those patients who had pre-existing comorbidity and who do not have.⁵⁴ This may be due to the co-morbidity type difference between the two study cases.

Limitation

Since our study was a retrospective study, we used secondary data. We used also low sample sample size and we analyzed only base line data. So, further study should be done with full follow up data.

Conclusion

COVID-19 infected patients frequently show clinical symptoms such as cough, shortness of breath, fever, headache, easy fatigue and Joint pain. The majority of the patients were also shown tachypnea, hypoxia and tachycardia. The most common co-morbidities of the COVID-19 patients were hypertension, type II DM, Tuberculosis, Cardiac disease, renal disease and Asthma. On arrival to the treatment center, most of the cases were severe, and also there were many moderate cases while few of them were mild. Having a normal body temperature, normal breathing rate, and severe disease status had statistically significant association with median recovery time. COVID-19 patients who had co-morbidity with chronic diseases and those that had no chronic diseases had statistically significant recovery probability difference between the age group of above 50 and 30–49 years. So, close follow up is required for patients admitted with severe disease status, even though all COVID-19 cases need care. These findings could help in designing of appropriate management strategy for patients under treatment.

Abbreviations

AHR, adjusted hazard ratio; ARDS, acute respiratory distress syndrome; CHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; HIV, human immunovirus; IRB, Institutional Review Board; LDH, lactate dehydrogenase; MI, myocardial infarction; RBM, RNA binding motive; RT-PCR, real time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNNPR, Southern Nations, Nationalities, and Peoples Region; SPSS, Statistical Package for the Social Sciences; UK, United Kingdom.

Ethics Approval and Consent to Participate

Ethical approval and waiver consent was obtained from the Institutional Review Board (IRB) of the Dilla University College of Medicine and Health sciences under the protocol unique number of duirb/002/21-10, and the permission from treatment center record room for data collection.

Data Sharing Statement

The datasets used during this study are available from the corresponding author when required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execusion, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountale for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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