

## RESEARCH ARTICLE

# COVID-19 disease severity and associated factors among Ethiopian patients: A study of the millennium COVID-19 care center

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## Abstract

### Background

The COVID-19 pandemic started a little later in Ethiopia than the rest of the world and most of the initial cases were reported to have a milder disease course and a favorable outcome. This changed as the disease spread into the population and the more vulnerable began to develop severe disease. Understanding the risk factors for severe disease in Ethiopia was needed to provide optimal health care services in a resource limited setting.

### Objective

The study assessed COVID-19 patients admitted to Millennium COVID-19 Care Center in Ethiopia for characteristics associated with COVID-19 disease severity.

### Methods

A cross-sectional study was conducted from June to August 2020 among 686 randomly selected patients. Chi-square test was used to detect the presence of a statistically significant difference in the characteristics of the patients based on disease severity (Mild vs Moderate vs Severe). A multinomial logistic regression model was used to identify factors associated with COVID-19 disease severity where Adjusted Odds ratio (AOR), 95% CIs for AOR and P-values were used for significance testing.

### Results

Having moderate as compared with mild disease was significantly associated with having hypertension ( $AOR = 2.30$ ,  $95\%CI = 1.27, 4.18$ ), diabetes mellitus ( $AOR = 2.61$ ,  $95\%CI = 1.31, 5.19$  for diabetes mellitus), fever ( $AOR = 6.12$ ,  $95\%CI = 2.94, 12.72$ ) and headache ( $AOR = 2.69$ ,  $95\%CI = 1.39, 5.22$ ). Similarly, having severe disease as compared with mild disease was associated with age group ( $AOR = 4.43$ ,  $95\%CI = 2.49, 7.85$  for 40–59 years and  $AOR = 18.07$ ,  $95\%CI = 9.29, 35.14$  for  $\geq 60$  years), sex ( $AOR = 1.84$ ,  $95\%CI = 1.12, 3.03$ ), hypertension ( $AOR = 1.97$ ,  $95\%CI = 1.08, 3.59$ ), diabetes mellitus ( $AOR = 3.93$ ,

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**Abbreviations:** CI, Confidence Interval; COVID-19, Coronavirus Disease 2019; FiO<sub>2</sub>, Fraction of Inspired Oxygen; LDH, Lactate Dehydrogenase; OR, Odds Ratio; PaO<sub>2</sub>, Partial Pressure of Oxygen; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO<sub>2</sub>, Saturation of Oxygen; RT-PCR, Real Time Polymerase Chain Reaction.

*95%CI = 1.96, 7.85*), fever (*AOR = 13.22, 95%CI = 6.11, 28.60*) and headache (*AOR = 4.82, 95%CI = 2.32, 9.98*). In addition, risk factors of severe disease as compared with moderate disease were found to be significantly associated with age group (*AOR = 4.87, 95%CI = 2.85, 8.32 for 40–59 years and AOR = 18.91, 95%CI = 9.84, 36.331 for ≥ 60 years*), fever (*AOR = 2.16, 95%CI = 1.29, 3.63*) and headache (*AOR = 1.79, 95%CI = 1.03, 3.11*).

## Conclusions

Significant factors associated with severe COVID-19 in Ethiopia are being older than 60 years old, male, a diagnosis of hypertension, diabetes mellitus, and the presence of fever and headache. This is consistent with severity indicators identified by WHO and suggests the initial finding of milder disease in Ethiopia may have been because the first people to get COVID-19 in the country were the relatively younger with fewer health problems.

## Introduction

The Coronavirus Infectious Disease 2019 (COVID-19) caused by the new coronavirus Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) has affected the entire world resulting in loss of millions of lives and causing a substantial burden on the health care system and the economy in general [1]. According to the World Health Organization (WHO) report, the first infected case was identified in Africa a little later than the rest of the world after it has already caused a notable morbidity and mortality in others [2].

In Ethiopia, the first case of COVID-19 was diagnosed two days after the WHO declared the disease to be a pandemic on March 11, 2020. According to the Ethiopian Federal Ministry of Health Daily COVID-19 report, as of October 30, 2021, there were a total of 364,960 infected cases with 425 cases under intensive care [3]. According to the report and studies conducted in Ethiopia the majority of the reported cases have milder disease presentations with favorable outcomes [3–5].

Studies show that having symptomatic disease and developing severe disease seems to be determined by socio-demographic characteristics including male sex and older age. Having a history of pre-existing co-morbid illness particularly hypertension, diabetes, severe asthma, cancer, renal disease, cardiovascular, cerebrovascular diseases, and other co-morbidities were also found to be predictors of severe disease [6–23]. This is also reported in studies conducted in Ethiopia [4, 5, 24–26].

Disease severity is also reported to be associated with lower oxygen saturation and abnormal laboratory markers including higher levels of leukocyte count, neutrophil count, high sensitivity C reactive protein, procalcitonin, ferritin, interleukin 2, 6 and 8 receptors, tumor necrosis factor  $\alpha$ , D-dimer, fibrinogen, lactate dehydrogenase, N-terminal pro-brain natriuretic peptide, cytokine, LDH and lower levels of CD4 count and deranged lymphocyte count [12, 16, 18, 27–31].

With the differing pattern in disease presentation, progression and outcome in Africa in general as compared with the rest of the world as observed so far and also considering the existing endemic disease pattern, conducting a study in Africa is crucial to understand the disease pattern in the local context. Because knowing the risk factors of developing severe disease is important as severe disease is associated with worse outcomes so that stratified and focused patient management and preventive practices can be provided which is a practical solution in

a resource limited country like Ethiopia where the health care infrastructure cannot meet the potentially growing demand of intensive care unit admission.

Therefore, the objective of this study was to identify the risk factors of disease severity among COVID-19 patients admitted to Millennium COVID-19 Care Center in Addis Ababa, Ethiopia.

## Materials and methods

### Study design, setting and population

An institution-based analytic cross-sectional study, following the STROBE guidelines for analytical cross-sectional studies, was conducted at Millennium COVID-19 Care Center (MCCC), a 1000 bed makeshift hospital in Addis Ababa, Ethiopia dedicated for isolating and treating COVID-19 cases [32]. The center was remodeled from Millennium Hall, a multipurpose recreational, meeting and exhibition center. It was the second COVID-19 treatment center and first remodeled COVID-19 treatment center in Ethiopia with the largest national bed capacity and remains to be the largest to which a majority of Ethiopian COVID-19 cases were admitted during the first few months of the pandemic." At the beginning, since there were few cases, the MCCC and also other Centers in the country were used as both a quarantine and treatment center in order to halt the transmission of the disease. Therefore, anyone who tested positive for SARS-Cov-2 gets admitted to COVID-19 Centers despite the age, disease severity, presence of symptoms and co-morbidity status.

The source population was all patients admitted to MCCC with a confirmed diagnosis of COVID-19 using RT-PCR from June to August 2020.

The study population was all selected COVID-19 patients who were on treatment and follow up at MCCC during the three month period and who fulfill the inclusion criteria.

### Sample size determination and sampling technique

The sample size to identify risk factors of disease severity was determined using a double population proportion formula with the assumptions of; 95% confidence interval, power of 80%, the proportion of males who had severe disease as 80%, proportion of females who had severe disease as 75% and considering a non-response rate of 10%. Therefore, the total sample size calculated becomes 689 COVID-19 patients. A simple random sampling method using table of random numbers was used to select the study participants, from the liaison admission registry, who were admitted from June to August 2020

### Eligibility criteria

All selected COVID-19 patients who were admitted to MCCC during the three months follow-up period and who consented to participate were included in the study. Assessment of disease severity, comorbidity and all other was made at admission. The study included all age groups. Comorbidities were recorded as either a pre-existing comorbidity or those which were diagnosed at admission.

### Operational definitions

**COVID-19 disease** [33]:

- **Mild disease:** characterized by fever, malaise, cough, upper respiratory symptoms, and/or less common features of COVID-19 (headache, loss of taste or smell etc. . .)

- **Moderate disease:** Patients with lower respiratory symptom/s. They may have infiltrates on chest X-ray. These patients are able to maintain oxygenation on room air.
- **Severe COVID-19 disease:** Includes patients who have developed complications. The following features can define severe illness.
  - Hypoxia:  $SPO_2 \leq 93\%$  on atmospheric air or  $PaO_2:FiO_2 < 300\text{mmHg}$  (SF ratio  $< 315$ )
  - Tachypnea: in respiratory distress or  $RR > 30$  breaths/minutes
  - More than 50% involvement seen on chest imaging

### Data collection procedures and quality assurance

An interviewer-administered questionnaire that consists of the variables of interest was developed from the patient registration and follow up form which was adopted from the WHO patient admission and management guideline and used at the center for patient follow up.

The data collection tool was pretested on 35 randomly selected patients and their medical charts which were not included in the final data collection and necessary amendment on the data collection tool was made.

Training on the basics of the questionnaire and data collection technique was given for ten data collectors (BSc nurses and General practitioners) and two supervisors (General practitioner and public health specialist).

Data consistency and completeness was checked before an attempt was made to enter the code and analyze the data.

### Statistical analysis

The extracted data were coded, entered into Epi-Info version 7.2.1.0, cleaned, stored, and exported to SPSS version 23.0 software for analysis. Categorical covariates were summarized using frequencies and percentages and numerical variables were summarized with a mean value. A Chi-square test/ Fischer's exact test was run to compare the underlying characteristics of the patients based on disease severity. A statistically significant difference was detected for variables with a P-value of  $\leq 0.05$ . The presence of multi-collinearity was checked for the independent variables fit on the final model and the VIF result ranges from 1.081 to 1.314 showing that there is no multi-collinearity issue in the final model.

The association between disease severity and determinant variables were analyzed using Multinomial Logistic Regression. Univariate analysis was done at 25% level of significance to screen out independent variables used in the multivariable multinomial Logistic regression model. The adequacy of the final model was assessed using goodness of fit test and the final model fitted the data well (Pearson  $\chi^2_{(118)} = 141.005$ , p-value = 0.073 and Deviance  $\chi^2_{(118)} = 134.542$ , p-value = 0.142). For the multinomial Logistic regression, 95% confidence interval for AOR was calculated and variables with p-value  $\leq 0.05$  were considered as statistically associated with COVID-19 disease severity at admission.

### Ethics approval

The study was conducted after obtaining ethical clearance from St. Paul's Hospital Millennium Medical College Institutional Review Board (Ref No. pm23/23). After assessing their level of consciousness, written informed consent was obtained from the participants and for those who were not conscious consent was obtained from family members. For minors, consent was obtained from parents or legal guardians. The study had no risk/negative consequence on

those who participated in the study. Medical record numbers were used for data collection and personal identifiers were not used in the research report. Access to the collected information was limited to the principal investigator and confidentiality was maintained throughout the project.

## Result

### Socio-demographic, co-morbid illness and disease related characteristics and comparison based on disease severity

From the 689 participants selected, information was collected from 686 patients making the response rate 99.5%. The median age of the participants was 40.0 (IQR, 30.0–57.3) years. The majority (63.1%) were males. Two hundred sixty-seven (38.9%) of the patients had a history of one or more co-morbid illnesses. The most common co-morbid illness in the study population was hypertension (21.1%), followed by diabetes mellitus (16.6%), cardiac disease (5.2%) and Asthma (4.7%), tuberculosis (1.7%). Other co-morbid illnesses like chronic kidney disease and neurologic disorder constituted less than 2% of the co-morbid illnesses reported. Twenty-five (3.6%) of the patients were Khat chewers and nine (1.3%) were smokers.

A statistically significant difference in disease severity was found among the different groups of patients by age group, sex, co-morbid illness, hypertension, and diabetes mellitus. A significant proportion of patients 40 to 59 years (29.4% Vs 29.9% Vs 40.6%,  $p$ -value = 0.0001) and  $\geq 60$  years (16.6% Vs 16.6% Vs 66.9%,  $p$ -value = 0.0001) presented with severe disease and the younger age group of  $< 40$  years presented with mild disease (46.2% Vs 41.1% Vs 12.7%,  $p$ -value = 0.0001). Based on sex, a significantly higher proportion of female patients had mild disease (41.1% Vs 31.2% Vs 27.7%,  $p$ -value = 0.021). On the contrary, males had severe disease (31.2% Vs 33.3% Vs 35.6%,  $p$ -value = 0.021). A significantly higher proportion of patients with one or more co-morbid illnesses had severe disease followed by moderate and then mild disease (20.6% Vs 30.3% Vs 49.1%,  $p$ -value = 0.0001). Similarly, patients with hypertension (17.2% Vs 29.7% Vs 53.1%,  $p$ -value = 0.0001) and diabetes (12.3% Vs 28.9% Vs 58.8%,  $p$ -value = 0.0001) had severe disease followed by moderate and then mild disease ([Table 1](#)).

### Presenting symptom related characteristics and comparison based on disease severity

The most common presenting symptom was cough (56.4%) followed by shortness of breath (26.9%), fatigue (23.2%), fever (20.9%), headache (16.5%), chest pain (16.1%), sore throat (13.7%), arthralgia (11.2%), myalgia (10.1%), and runny nose (5.1%).

As shown in [Table 2](#), the chi-square test result shows that a significantly higher proportion of patients with any of the above presenting symptoms had severe disease, followed by moderate and then mild disease ([Table 2](#)).

### Results of factors associated with COVID-19 disease severity (Mild Vs Moderate Vs Severe)

Based on the result of the Univariate analysis at 25% level of significance; Age group, sex, hypertension, diabetes mellitus, fever, and headache were found to be significantly associated with COVID-19 disease severity (Mild Vs Moderate Vs Severe).

On the multivariable multinomial logistic regression at 5% level of significance; age group, hypertension, diabetes mellitus, fever, and headache were found to be significantly associated with COVID-19 disease severity. Accordingly, after adjusting for other covariates, for patients in the age range of 40 to 59 years and  $\geq 60$  years, the odds of having severe disease as

**Table 1. Socio-demographic, co-morbid illness, disease related characteristics and comparison based on disease severity among patients (n = 686).**

Variable	Mild (n = 239) (%)	Moderate (n = 223) (%)	Severe (n = 224) (%)	Total (%)	P-value
<b>Age</b>					
< 40	156 (65.3)	139 (62.3)	43 (19.2)	338 (49.3)	<b>0.0001*</b>
40–59	58 (24.3)	59 (26.5)	80 (35.7)	197 (28.7)	
≥ 60	25 (10.4)	25 (11.2)	101 (45.1)	151 (22.0)	
<b>Sex</b>					
Female	104 (43.5)	79 (35.4)	70 (31.2)	253 (36.9)	<b>0.021*</b>
Male	135 (56.5)	144 (64.6)	154 (68.8)	433 (63.1)	
<b>Co-morbid illness</b>					
Yes	55 (23.0)	81 (36.3)	131 (58.5)	267 (38.9)	<b>0.0001*</b>
No	184 (76.9)	142 (63.7)	93 (41.5)	419 (61.1)	
<b>Hypertension</b>					
Yes	25 (10.5)	43 (19.2)	77 (34.4)	145 (21.1)	<b>0.0001*</b>
No	214 (89.5)	180 (80.7)	147 (65.6)	541 (78.8)	
<b>Diabetes Mellitus</b>					
Yes	14 (5.9)	33 (14.8)	67 (29.9)	114 (16.6)	<b>0.0001*</b>
No	225 (94.1)	190 (85.2)	157 (70.1)	572 (83.3)	
<b>Asthma</b>					
Yes	9 (3.8)	9 (4.0)	14 (6.3)	32 (4.7)	0.387
No	230 (96.2)	214 (95.9)	210 (93.8)	654 (95.3)	
<b>Khat chewing</b>					
Yes	5 (2.1)	8 (3.6)	12 (5.4)	25 (3.6)	0.173
No	234 (97.9)	215 (96.4)	212 (94.6)	661 (96.4)	

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**Table 2. Presenting symptom related characteristics and comparison based on disease severity among COVID-19 patients (n = 686).**

Variables	Mild (n = 239) (%)	Moderate (n = 223) (%)	Severe (n = 224) (%)	Total (%)	P-value
<b>Fever</b>					
Yes	10 (4.2)	53 (23.8)	81 (36.2)	144 (20.9)	<b>0.0001*</b>
No	229 (95.8)	170 (76.2)	143 (63.8)	542 (79.1)	
<b>Sore throat</b>					
Yes	14 (5.9)	40 (17.9)	40 (17.9)	94 (13.7)	<b>0.0001*</b>
No	225 (94.1)	183 (82.1)	184 (82.1)	592 (86.3)	
<b>Runny nose</b>					
Yes	3 (1.3)	16 (7.2)	16 (7.1)	35 (5.1)	<b>0.004*</b>
No	236 (98.7)	207 (92.8)	208 (92.9)	651 (94.9)	
<b>Myalgia</b>					
Yes	7 (2.9)	25 (11.2)	37 (16.5)	69 (10.1)	<b>0.0001*</b>
No	232 (97.1)	198 (88.8)	187 (83.4)	617 (89.9)	
<b>Arthralgia</b>					
Yes	9 (3.8)	23 (10.3)	45 (20.1)	77 (11.2)	<b>0.0001*</b>
No	230 (96.2)	200 (89.7)	179 (79.9)	609 (88.8)	
<b>Fatigue</b>					
Yes	11 (4.6)	42 (18.8)	106 (47.3)	159 (23.2)	<b>0.0001*</b>
No	228 (95.4)	181 (81.2)	118 (52.7)	527 (76.8)	
<b>Headache</b>					
Yes	15 (6.3)	42 (18.8)	56 (25.0)	113 (16.5)	<b>0.0001*</b>
No	224 (93.7)	181 (81.2)	168 (75.0)	573 (83.5)	

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compared with mild disease were 4.428 and 18.070 times than patients < 40 years, respectively (AOR = 4.43, 95% CI = 2.49, 7.85, p-value = 0.0001 for 40–59 years and AOR = 18.07, 95% CI = 9.29, 35.14, p-value = 0.0001 for  $\geq 60$  years). Similarly, the odds of having severe disease as compared with moderate disease among patients 40 to 59 years and  $\geq 60$  years were 4.87 and 18.906 times than patients < 40 years, respectively (AOR = 4.87, 95% CI = 2.85, 8.32, p-value = 0.0001 for 40–59 years and AOR = 18.91, 95% CI = 9.84, 36.33, p-value = 0.0001 for  $\geq 60$  years). But age group didn't show a statistically significant association with disease severity between moderate and mild cases.

A statistically significant association of sex with disease severity was found only between severe cases as compared with mild. Being male was associated with a 1.84 odds of having severe disease as compared with mild disease than females (AOR = 1.84, 95% CI = 1.12, 3.03, p-value = 0.016).

Regarding co-morbid illness, having hypertension and diabetes was significantly associated with disease severity between moderate Vs mild and moderate Vs severe disease, but not between severe Vs moderate disease. For patients with hypertension and diabetes, the odds of having moderate disease as compared with mild disease were 2.30 and 2.61 times compared to patients with no such illnesses, respectively (AOR = 2.30, 95% CI = 1.27, 4.18, p-value = 0.006 for hypertension and AOR = 2.61, 95% CI = 1.31, 5.19, p-value = 0.007 for diabetes mellitus). Similarly, the odds of having severe disease as compared with mild disease for hypertensive and diabetic patients were 1.97 and 3.93 times patients with no such illnesses, respectively (AOR = 1.97, 95% CI = 1.08, 3.59, p-value = 0.028 for hypertension and AOR = 3.93, 95% CI = 1.96, 7.85, p-value = 0.0001 for diabetes mellitus).

Concerning presenting symptoms, having fever and headache was significantly associated with disease severity; moderate Vs mild, severe Vs mild, and severe Vs moderate. The odds of having moderate disease as compared with mild disease for patients with fever and headache were 6.12 and 2.69 times than patients with no such symptoms, respectively (AOR = 6.12, 95% CI = 2.94, 12.72, p-value = 0.0001 for fever; AOR = 2.69, 95% CI = 1.39, 5.22, p-value = 0.003 for headache). The odds of having severe disease as compared with mild disease for patients with fever and headache were 13.22 and 4.82 times than patients with no such symptoms, respectively (AOR = 13.22, 95% CI = 6.11, 28.60, p-value = 0.0001 for fever; AOR = 4.82, 95% CI = 2.32, 9.97, p-value = 0.0001 for headache). Similarly, the odds of having severe disease as compared with moderate disease for patients with fever and headache were 2.16 and 1.79 times compared to patients with no such symptoms, respectively (AOR = 2.16, 95% CI = 1.29, 3.63, p-value = 0.004 for fever; AOR = 1.79, 95% CI = 1.03, 3.11, p-value = 0.039 for headache) ([Table 3](#)).

## Discussion

Based on our findings from the 1000 bed makeshift hospital in Addis Ababa, we found some evidence of association between having severe COVID and age group, hypertension, diabetes mellitus, fever, and headache.

Age group was one of the identified significant factor associated with disease severity. For patients in the age range of 40 to 59 years and 60 years and older, the odds of having severe disease as compared with mild and moderate disease was found to be higher compared with those patients younger than 40 years. But age group didn't show a significant association with disease severity between moderate and mild cases. That means patients 40 years and above are at risk of developing more severe disease with the risk being much higher (18 fold) for those 60 years and above. This could be associated with the vulnerable nature of old age group due to the natural diminishing of the body's defense mechanism and also the increased possibility of

Table 3. Results for the final multinomial logistic regression model among COVID-19 patients (n = 686).

Variable	Moderate (Vs Mild)		Severe (Vs Mild)		Severe (Vs Moderate)	
	AOR (95% CI)	P-value	AOR (95% CI)	P-value	AOR (95% CI)	P-value
<b>Age group (in years)</b>						
< 40	1		1		1	
40–59	0.91 (0.56, 1.48)	0.701	4.43 (2.49, 7.85)	0.0001*	4.87 (2.85, 8.32)	0.0001*
≥ 60	0.96 (0.49, 1.86)	0.894	18.07 (9.29, 35.14)	0.0001*	18.91 (9.84, 36.33)	0.0001*
<b>Sex</b>						
Female	1		1		1	
Male	1.17 (0.78, 1.75)	0.455	1.84 (1.12, 3.03)	0.016*	1.58 (0.97, 2.56)	0.064
<b>Hypertension</b>						
No	1		1		1	
Yes	2.30 (1.27, 4.18)	0.006*	1.97 (1.08, 3.59)	0.028*	0.85 (0.49, 1.47)	0.568
<b>Diabetes Mellitus</b>						
No	1		1		1	
Yes	2.61 (1.31, 5.19)	0.007*	3.93 (1.96, 7.85)	0.0001*	1.51 (0.88, 2.57)	0.134
<b>Fever</b>						
No	1		1		1	
Yes	6.12 (2.94, 12.72)	0.0001*	13.22 (6.11, 28.60)	0.0001*	2.16 (1.29, 3.63)	0.004*
<b>Headache</b>						
No	1		1		1	
Yes	2.69 (1.39, 5.22)	0.003*	4.82 (2.32, 9.98)	0.0001*	1.79 (1.03, 3.11)	0.039*

**Note:** COR, Crude Odds ratio; AOR, Adjusted Odds ratio; CI, Confidence interval; \* Statistically significant.

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having concomitant comorbid illnesses that might not even be diagnosed, especially in the developing world with inadequate screening services, that further compromises the immune system. In another study conducted in our Center, older patients were found to be at risk of developing symptomatic infection compared to the younger group showing that older patients are susceptible to have a worse disease presentation and severity that could lead to a worse prognosis [4]. In addition, studies conducted in China and Saudi Arabia also showed that aged people are more susceptible to development of severe disease and unfavorable outcome [12, 27, 31, 34, 35]. Being male was associated with a 1.842 odds of having severe disease as compared with mild disease than females. This significant difference in disease severity could be attributed to the identified difference in the disease biochemical activity between the two sexes showing that Angiotensin-converting enzyme 2, the receptor used by SARS-CoV-2, is found to be naturally abundant among males making it more convenient for high viral replication and development of symptomatic and severe disease compared to females [36–42].

For patients with hypertension and diabetes, the odds of having moderate and severe disease as compared with mild disease were higher compared to patients with no such illnesses. As explained above, since having one or more co-morbid illness results in a decreased immune defense mechanism of the body, it increases the patients' probability of developing a disease from any infectious agent. This effect is accelerated if the comorbid illness/s is not well controlled. Furthermore, patients with comorbidity tend to be older, that in-turn adds to the existing decrease in immunity. This finding is also supported by other studies conducted in Ethiopia, China, England and the US [5, 12, 26, 27, 34, 35].

In addition, the other important factors that determine disease severity were fever and headache. The odds of having moderate and severe disease as compared with mild disease and also the odds of having severe disease as compared with moderate disease for patients with



fever and headache were higher than patients with no such symptoms. That means, having symptoms from SARS-CoV-2 infection are associated with developing a more severe disease as compared to the asymptomatic patients. Though these symptoms are not directly related to the disease severity classification in the study set up; like symptoms of cough, shortness of breath, and chest pain, they are found to be significant factors associated with disease severity. This implies that non-respiratory symptoms also might have a predictive value in disease categorization. This is also demonstrated by other studies in Ethiopia [4, 5, 24–26].

When interpreting these findings, it is important to consider both its strength and limitation. Its strength is that it included a robust sample size from the most representative care center in the country. Its main limitation was that, based on prior reports, important variables that were potential risk factors for disease severity were not consistently available for all patients so could not be considered in the final model. This included Body Mass Index (BMI), as well as some laboratory and radiologic data.

## Conclusion

In Ethiopia, being 40 years and older (especially those 60 years and older), male, with a diagnosis of hypertension or diabetes, and having fever and headache were associated with severe COVID-19 disease. This suggests the initial cases in Ethiopia may have been milder because it affected younger people with fewer risk factors. We recommend a multicenter study that includes additional clinical, laboratory and radiologic data to further understand COVID-19 in Ethiopia.

## Supporting information

### S1 Questionnaire.

(ZIP)

### S1 Data.

(SAV)

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## References

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020. <https://doi.org/10.1016/j.jaut.2020.102433> PMID: 32113704
2. WHO. WHO Africa news: A second COVID-19 case is confirmed in Africa. February 25, 2020.
3. Ethiopian Federal Ministry of Health. National COVID-19 Daily report. October 30, 2021.
4. Leulseged TW, Alemahu DG, Hassen IS, Maru EH, Zewde WC, Chamiso NW, et al. Factors associated with development of symptomatic disease in Ethiopian COVID-19 patients: a case-control study. *BMC infectious diseases.* 2021; 21(1):759. <https://doi.org/10.1186/s12879-021-06465-1> PMID: 34353283
5. Leulseged TW, Hassen IS, Maru EH, Zewsde WC, Chamiso NW, Bayisa AB. Characteristics and outcome profile of hospitalized African patients with COVID-19: The Ethiopian context. *PLoS one.* 2021; 16(11):e0259454. <https://doi.org/10.1371/journal.pone.0259454> PMID: 34752481
6. Bezzio C, Saibeni S, Variola A, Allocca M, Massari A, Gerardi V, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut.* 2020 Apr 30. <https://doi.org/10.1136/gutjnl-2020-321411> PMID: 32354990
7. Meng Y, Wu P, Lu W, Liu K, Ma K, Huang L, et al. Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: A retrospective study of 168 severe patients. *PLoS Pathog.* 2020 April 28; 16(4). <https://doi.org/10.1371/journal.ppat.1008520> PMID: 32343745
8. Mi B, Chen L, Xiong Y, Xue H, Zhou W, Liu G. Characteristics and Early Prognosis of COVID-19 Infection in Fracture Patients. *Bone Joint Surg Am.* 2020 Apr 01 <https://doi.org/10.2106/JBJS.20.00390> PMID: 32379114
9. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. *J Am Soc Nephrol.* 2020 Apr 28. <https://doi.org/10.1681/ASN.2020030276> PMID: 32345702
10. Sun L, Shen L, Fan J, Gu F, Hu M, An Y, et al. Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China. *J Med Virol* 2020 May 05. <https://doi.org/10.1002/jmv.25966> PMID: 32369208
11. Wang F, Yang Y, Dong K, Yan Y, Zhang S, Ren H, et al. CLINICAL CHARACTERISTICS OF 28 PATIENTS WITH DIABETES AND COVID-19 IN WUHAN, CHINA. *Endocr Pract.* 2020 May 01.
12. Li Xiaochen, Xu Shuyun, Yu Muqing, Wang Ke, Tao Yu, Zhou Ying, et al. Risk factors for severity and mortality in dult COVID-19 inpatients in Wuhan. *J ALLERGY CLIN IMMUNOL.* 2020; 146:110–8. <https://doi.org/10.1016/j.jaci.2020.04.006> PMID: 32294485
13. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes *BMJ Open Diabetes Res Care.* 2020 April; 8(1).
14. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Clinical characteristics and outcomes of cancer patients with COVID-19. *J Med Virol* 2020 May 05.
15. van Marcke C, Honoré N, van der Elst A, Beyaert S, Derouane F, Dumont C, et al. Safety of systemic anti-cancer treatment in oncology patients with non-severe COVID-19: a cohort study. *BMC Cancer.* 2021; 21(1):578. <https://doi.org/10.1186/s12885-021-08349-8> PMID: 34016086
16. Alimohamadi Y, Sepandi M, Taghdir M, Hosamirudsari H. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. *Journal of preventive medicine and hygiene.* 2020; 61(3):E304–e12. <https://doi.org/10.15167/2421-4248/jpmh2020.61.3.1530> PMID: 33150219
17. Falzone L, Gattuso G, Tsatsakis A, Spandidos DA, Libra M. Current and innovative methods for the diagnosis of COVID-19 infection (Review). *International journal of molecular medicine.* 2021; 47(6): 100. <https://doi.org/10.3892/ijmm.2021.4933> PMID: 33846767
18. Pennisi M, Lanza G. SARS-CoV-2 and the Nervous System: From Clinical Features to Molecular Mechanisms. 2020; 21(15).

19. Taghizadeh-Hesary F, Porouhan P, Soroosh D, PeyroShabany B, Shahidsales S, Keykhosravi B, et al. COVID-19 in Cancer and Non-cancer Patients. *Int J Cancer Manag.* 2021; 14(4):e110907.
20. Siavashpour Z, Taghizadeh-Hesary F, Rakhsha A. Recommendations on Management of Locally Advanced Rectal Cancer During the COVID-19 Pandemic: an Iranian Consensus. *Journal of gastrointestinal cancer.* 2020; 51(3):800–4. <https://doi.org/10.1007/s12029-020-00454-4> PMID: 32656628
21. Xu S, Cheng X, Pan Z, Song Q, Wang Y, Xiong J, et al. Cancer patient management strategy in a Cancer Center of Zhejiang, China during the COVID-19 pandemic. *BMC Cancer.* 2020; 20(1):1194. <https://doi.org/10.1186/s12885-020-07577-8> PMID: 33287747
22. Rakhsha A, Azghandi S, Taghizadeh-Hesary F. COVID-19 pandemic and patients with cancer: The protocol of a Clinical Oncology center in Tehran, Iran. *Reports of Practical Oncology & Radiotherapy.* 2020; 25(5):765–7. <https://doi.org/10.1016/j.rpor.2020.07.001> PMID: 32765192
23. Fadavi P, Houshyari M, Yousefi Kashi AS, Jarrahi AM, Roshanmehr F, Broomand MA, et al. Review on the Oncology Practice in the Midst of COVID-19 Crisis: The Challenges and Solutions. *Asian Pacific Journal of Cancer Prevention.* 2021; 22(1):19–24. <https://doi.org/10.31557/APJCP.2021.22.1.19> PMID: 33507674
24. Leulseged TW, Maru EH, Hassen IS, Zewde WC, Chamiso NW, Abebe DS, et al. Predictors of death in severe COVID-19 patients at millennium COVID-19 care center in Ethiopia: a case-control study. *PAMJ.* 2021;38. <https://doi.org/10.11604/pamj.2021.38.351.28831> PMID: 34367430
25. Leulseged TW, Hassen IS, Ayele BT, Tsegay YG, Abebe DS, Edo MG, et al. Laboratory biomarkers of COVID-19 disease severity and outcome: Findings from a developing country. *PloS one.* 2021; 16(3): e0246087. <https://doi.org/10.1371/journal.pone.0246087> PMID: 33720944
26. Leulseged TW, Hassen IS, Edo MG, Abebe DS, Maru EH, Zewde WC, et al. Duration of Supplemental Oxygen Requirement and Predictors in Severe COVID-19 Patients in Ethiopia: A Survival Analysis. *Ethiopian journal of health sciences.* 2021; 31(4):699–708. <https://doi.org/10.4314/ejhs.v31i4.3> PMID: 34703168
27. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J.* 2020;2020(55: 2000524).
28. Feng P, Lian Y, Yuncheng L, Bo L, Lin L, Tianhe Y, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study *Int J Med Sci.* 2020; 17(9):1281–92. <https://doi.org/10.7150/ijms.46614> PMID: 32547323
29. Yang Y, Shen C, Li J, Yuan J, Wei J, Huang F, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *J Allergy Clin Immunol* 2020 Apr 29. <https://doi.org/10.1016/j.jaci.2020.04.027> PMID: 32360286
30. Grant MC, Geoghegan L. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. 2020; 15(6):e0234765. <https://doi.org/10.1371/journal.pone.0234765> PMID: 32574165
31. Abdelsalam M, Althaqafi RMM, Assiri SA, Althagafi TM, Althagafi SM, Fouda AY, et al. Clinical and Laboratory Findings of COVID-19 in High-Altitude Inhabitants of Saudi Arabia. *Frontiers in Medicine.* 2021; 8(488). <https://doi.org/10.3389/fmed.2021.670195> PMID: 34055842
32. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of internal medicine.* 2007; 147(8):573–7. <https://doi.org/10.7326/0003-4819-147-8-200710160-00010> PMID: 17938396
33. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance. Geneva: March 2020
34. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed M, et al. Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US. *JAMA Intern Med.*2020;e203596. <https://doi.org/10.1001/jamainternmed.2020.3596> PMID: 32667668
35. Williamson E.J., Walker A.J., Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 584:430–6 (2020). <https://doi.org/10.1038/s41586-020-2521-4> PMID: 32640463
36. Gavin YO, Marc AP. Plasma angiotensin-converting enzyme 2: novel biomarker in heart failure with implications for COVID-19. *European Heart Journal.* 14 May 2020; 41(19):1818–20. <https://doi.org/10.1093/eurheartj/ehaa414> PMID: 32388547
37. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner A, et al. Angiotensin converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin–angiotensin system. *Circ Res.* 2020.

38. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci.* 2020; 63:364–74. <https://doi.org/10.1007/s11427-020-1643-8> PMID: 32048163
39. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest* 2009; 39:618–25. <https://doi.org/10.1111/j.1365-2362.2009.02153.x> PMID: 19453650
40. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. *N Engl J Med.* 2020; 382:1653–9. <https://doi.org/10.1056/NEJMs2005760> PMID: 32227760
41. Wang K, Gheblawi M, GY O. Angiotensin converting enzyme 2: a double-edged sword. *Circulation.* 2020. <https://doi.org/10.1161/CIRCULATIONAHA.120.047049> PMID: 32213097
42. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science of the Total Environment.* 2020; 367:1444–8. <https://doi.org/10.1126/science.abb2762> PMID: 32132184