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COVID-19 Disease Severity and Determinants among Ethiopian Patients: A study of the Millennium COVID-19 Care Center

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ABSTRACT

Background: Understanding determinants of developing severe COVID-19 disease is important as studies show that severe disease is associated with worse outcomes.

Objective: The study aimed to assess the determinants of COVID-19 disease severity among COVID-19 patients admitted to Millennium COVID-19 Care Center in Ethiopia.

Methods: A cross-sectional study was conducted from June to August 2020 among randomly selected 686 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), where p-value of <0.05 was considered as having a statistically significant difference. A Multivariable multinomial logistic regression model was used to assess the presence of a significant association between the independent variables and COVID-19 disease severity where Adjusted Odds ratio (AOR), 95% CIs for AOR and P-values were used for testing significance and interpretation of results.

Results: Having moderate as compared with mild disease was significantly associated with having hypertension *(AOR= 2.302, 95% CI= 1.266, 4.184, p-value=0.006), diabetes mellitus (AOR=2.607, 95% CI= 1.307, 5.198, p-value=0.007 for diabetes mellitus), fever (AOR= 6.115, 95% CI= 2.941, 12.716, p-value=0.0001)* and headache *(AOR= 2.695, 95% CI= 1.392, 5.215, p-*

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value=0.003). Similarly, having severe disease as compared with mild disease was associated with age group *(AOR= 4.428, 95% CI= 2.497, 7.853, p-value=0.0001 for 40-59 years and AOR=18.070, 95% CI=9.292, 35.140, p-value=0.0001 for ≥ 60 years)*, sex (*AOR=1.842, 95% CI=1.121, 3.027, p-value=0.016)*, hypertension *(AOR= 1.966, 95% CI= 1.076, 3.593, p-value=0.028)*, diabetes mellitus *(AOR= 3.926, 95% CI= 1.964, 7.847, p-value=0.0001)*, fever *(AOR= 13.218, 95% CI= 6.109, 28.601, p-value=0.0001)* and headache *(AOR= 4.816, 95% CI= 2.324, 9.979, p-value=0.0001)*. In addition, determinants of severe disease as compared with moderate disease were found to be age group *(AOR= 4.871, 95% CI= 2.854, 8.315, p-value=0.0001 for 40-59 years and AOR= 18.906, 95% CI= 9.838, 36.334, p-value=0.0001 for ≥ 60 years)*, fever *(AOR= 2.161, 95% CI= 1.286, 3.634, p-value=0.004)* and headache *(AOR= 1.787, 95% CI= 1.028, 3.107, p-value=0.039).*

Conclusions: Being old, male sex, hypertension, diabetes mellitus, and having symptoms of fever and headache were found to be determinants of developing a more severe COVID-19 disease category. We recommend a better preventive practice to be set in place so that these groups of patients can be protected from acquiring the disease. And for those who are already infected, a more careful follow-up and management should be given so that complication and death can be prevented. Furthermore, considering the above non respiratory symptoms as disease severity indicator could be important.

Keywords: COVID-19 Severity, determinants, cross-sectional, multinomial logistic Regression, Ethiopia.

INTRODUCTION

In Ethiopia, the first case of COVID-19 was diagnosed 2 days after the World Health Organization has 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 2, 2020, there were a total of 44, 101 active cases with 296 critical patients[1].

Studies show that 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[2-10].

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 α, D-dimer, fibrinogen, lactate dehydrogenase, N-terminal pro-brain natriuretic peptide, cytokine, LDH and lower levels of CD4 count and deranged lymphocyte count [8,11-13].

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Knowing determinants of developing severe disease is important as severe disease is associated with worse outcome so that stratified and focused patient management and preventive practices can be provided.

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

METHODS AND MATERIALS

Study Design, Setting and Population

An institution-based cross-sectional study was conducted at Millennium COVID-19 Care Center (MCCC), a 1000 bed makeshift hospital in Addis Ababa, Ethiopia.

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 full fill the inclusion criteria.

Sample Size Determination and Sampling Technique

The sample size to identify determinants 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 0.80, proportion of females who had non-severe disease as 0.75 and considering a non-response rate of 10%. Therefore, the total sample size calculated becomes 689 COVID-19 patients.

A simple random sampling method was used to select the study participants.

Eligibility criteria

All 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.

Operational Definitions

COVID-19 disease [14]**:**

- **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.

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- Hypoxia: SPO2 ≤ 93% on atmospheric air or PaO2:FiO2 < 300mmHg (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 and used to collect the necessary data from the patients and their medical charts.

The data collection tool was pretested on 5% of 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.

Data Management and 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 was run to compare the underlying characteristics of the patients based on disease severity. The assumption of Chi-square test, that no cell should have an expected frequency of less than five was checked before the analysis, and the assumption was met. A statistically significant difference was detected for variables with a P-value of ≤ 0.05.

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 $x^2_{(118)}$ =141.005, p-value = 0.073 and Deviance $x^2_{(118)}$ =134.542, p-value = 0.142). For the multinomial Logistic regression, 95% confidence interval for AOR was calculated and variables with p-value ≤ 0.05 were considered as statistically associated with COVID-19 disease severity at admission.

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RESULT

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

From the 689 samples selected, information was collected from 686 patients making the response rate 99.5%. Almost half (49.3%) of the patients were less than 40 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 commonest co-morbid illness in the study population was hypertension (21.1%), followed by diabetes mellitus (16.6%) and Asthma (4.7%). Twenty-five (3.6%) of the patients were Khat chewers.

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 ≥ 60 years (16.6% Vs 16.6% Vs 66.9%, p-value=0.0001) had severe disease and the younger age group of < 40 years had 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**)

Table 1: Socio-demographic, preexisting co-morbid illness and disease related characteristics and comparison based on disease severity among COVID-19 patients (n=686)

Variable	Mild (%)	Moderate (%)	Severe (%)	Total (%)	P-value
Age					
< 40	156 (46.2)	139 (41.1)	43 (12.7)	338 (49.3)	**0.0001***
40-59	58 (29.4)	59 (29.9)	80 (40.6)	197 (28.7)	
≥ 60	25 (16.6)	25 (16.6)	101 (66.9)	151 (22.0)	
Sex					
Female	104 (41.1)	79 (31.2)	70 (27.7)	253 (36.9)	**0.021***
Male	135 (31.2)	144 (33.3)	154 (35.6)	433 (63.1)	
Co-morbid illness					
Yes	55 (20.6)	81 (30.3)	131 (49.1)	267 (38.9)	**0.0001***
No	184 (43.9)	142 (33.9)	93 (22.2)	419 (61.1)	
Hypertension					
Yes	25 (17.2)	43 (29.7)	77 (53.1)	145 (21.1)	**0.0001***

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No	214 (39.6)	180 (33.3)	147 (27.2)	541 (78.8)	
Diabetes Mellitus					
Yes	14 (12.3)	33 (28.9)	67 (58.8)	114 (16.6)	**0.0001***
No	225 (39.3)	190 (33.2)	157 (27.4)	572 (83.3)	
Asthma					
Yes	9 (28.1)	9 (28.1)	14 (43.8)	32 (4.7)	0.387
No	230 (35.2)	214 (32.7)	210 (32.1)	654 (95.3)	
Khat chewing					
Yes	5 (20.0)	8 (32.0)	12 (48.0)	25 (3.6)	0.173
No	234 (35.4)	215 (32.5)	212 (32.1)	661 (96.4)	

Presenting symptom related characteristics and comparison based on disease severity

More than half (64.7%) of the study population had one or more symptoms during the disease course. The majority had cough (56.4%), 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 sever disease, followed by moderate and then mild disease. (**Table 2**)

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

Variables	Mild (%)	Moderate (%)	Severe (%)	Total (%)	P-value
Presence of symptom					
Symptomatic	45 (10.1)	185 (41.7)	214 (48.2)	444 (64.7)	**0.0001***
Asymptomatic	194 (80.2)	38 (15.7)	10 (4.1)	242 (35.3)	
Fever					
Yes	10 (6.9)	53 (36.8)	81 (56.3)	144 (20.9)	**0.0001***
No	229 (42.3)	170 (31.4)	143 (26.4)	542 (79.1)	
Sore throat					
Yes	14 (14.9)	40 (42.6)	40 (42.6)	94 (13.7)	**0.0001***
No	225 (38.0)	183 (30.9)	184 (31.1)	592 (86.3)	
Runny nose					
Yes	3 (8.6)	16 (45.7)	16 (45.7)	35 (5.1)	**0.004***
No	236 (36.3)	207 (31.8)	208 (32.0)	651 (94.9)	

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Myalgia					
Yes	7 (10.1)	25 (36.2)	37 (53.6)	69 (10.1)	**0.0001***
No	232 (37.6)	198 (32.1)	187 (30.3)	617 (89.9)	
Arthralgia					
Yes	9 (11.7)	23 (29.9)	45 (58.4)	77 (11.2)	**0.0001***
No	230 (37.8)	200 (32.8)	179 (29.4)	609 (88.8)	
Fatigue					
Yes	11 (6.9)	42 (26.4)	106 (66.7)	159 (23.2)	**0.0001***
No	228 (43.3)	181 (34.3)	118 (22.4)	527 (76.8)	
Headache					
Yes	15 (13.3)	42 (37.2)	56 (49.6)	113 (16.5)	**0.0001***
No	224 (39.1)	181 (31.6)	168 (29.3)	573 (83.5)	

Results of determinants of 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 ≥ 60 years, the odds of having severe disease as compared with mild disease were 4.428 and 18.070 times than patients < 40 years, respectively (AOR= 4.428, 95% CI= 2.497, 7.853, p-value=0.0001 for 40-59 years and AOR=18.070, 95% CI= 9.292, 35.140, p-value=0.0001 for ≥ 60 years). Similarly, the odds of having severe disease as compared with moderate disease among patients 40 to 59 years and ≥ 60 years were 4.871 and 18.906 times than patients < 40 years, respectively (AOR= 4.871, 95% CI= 2.854, 8.315, p-value=0.0001 for 40-59 years and AOR= 18.906, 95% CI= 9.838, 36.334, p-value=0.0001 for ≥ 60 years). But age group didn't show a significant association with disease severity between moderate and mild cases.

A significant association of sex with disease severity was found only between severe cases as compared with mild. Being male was associated with a 1.842 odds of having severe disease as compared with mild disease than females (AOR=1.842, 95% CI=1.121, 3.027, 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 2.302 and 2.607 times compared to patients with no such illnesses, respectively (AOR= 2.302, 95% CI= 1.266, 4.184, p-value=0.006

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for hypertension and AOR= 2.607, 95% CI= 1.307, 5.198, 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 1.966 and 3.926 times patients with no such illnesses, respectively (AOR= 1.966, 95% CI= 1.076, 3.593, p-value=0.028 for hypertension and AOR= 3.926, 95% CI= 1.964, 7.847, p-value=0.0001 for diabetes mellitus).

Concerning presenting symptom, 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 6.115 and 2.695 times than patients with no such symptoms, respectively (AOR= 6.115, 95% CI= 2.941, 12.716, p-value=0.0001 for fever; AOR= 2.695, 95% CI= 1.392, 5.215, p-value=0.003 for headache). The odds of having severe disease as compared with mild disease for patients with fever and headache were 13.218 and 4.816 times than patients with no such symptoms, respectively (AOR= 13.218, 95% CI= 6.109, 28.601, p-value=0.0001 for fever; AOR= 4.816, 95% CI= 2.324, 9.979, p-value=0.0001 for headache). Similarly, the odds of having severe disease as compared with mild disease for patients with fever and headache were 2.161 and 1.787 times compared to patients with no such symptoms, respectively (AOR= 2.161, 95% CI= 1.286, 3.634, p-value=0.004 for fever; AOR= 1.787, 95% CI= 1.028, 3.107, p-value=0.039 for headache). (**Table 3**)

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**
Age group (in years)						
< 40	1		1		1	
40-59	0.909 (0.559, 1.478)	0.701	**4.428 (2.497, 7.853)**	**0.0001***	**4.871 (2.854, 8.315)**	**0.0001***
≥ 60	0.956 (0.490, 1.863)	0.894	**18.070 (9.292, 35.140)**	**0.0001***	**18.906 (9.838, 36.334)**	**0.0001***
Sex						
Female	1		1		1	
Male	1.167 (0.778, 1.750)	0.455	**1.842 (1.121, 3.027)**	**0.016***	1.578 (0.973, 2558)	0.064
Hypertension						
No	1		1		1	
Yes	**2.302 (1.266, 4.184)**	**0.006***	**1.966 (1.076, 3.593)**	**0.028***	0.854 (0.497, 1.467)	0.568
Diabetes Mellitus						

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No	1		1		1	
Yes	**2.607 (1.307, 5.198)**	**0.007***	**3.926 (1.964, 7.847)**	**0.0001***	1.506 (0.882, 2.572)	0.134
Fever						
No	1		1		1	
Yes	**6.115 (2.941, 12.716)**	**0.0001***	**13.218 (6.109, 28.601)**	**0.0001***	**2.161 (1.286, 3.634)**	**0.004***
Headache						
No	1		1		1	
Yes	**2.695 (1.392, 5.215)**	**0.003***	**4.816 (2.324, 9.979)**	**0.0001***	**1.787 (1.028, 3.107)**	**0.039***

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

DISCUSSION

The current study tried to assess the determinants of COVID-19 disease severity among patients admitted to Millennium COVID-19 Care Center in Ethiopia. The chi-square test result shows that developing a more sever disease category was observed among older age groups, male sex, pre-existing one or more co-morbid illness history, hypertension, diabetes mellitus, fatigue, fever, headache, sorethroat, arthralgia, myalgia, and runny nose. This shows that old age, male sex, comorbid illness, and having any symptoms could be used as an indicator of the possibility of developing more severe disease.

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.

Age group was one of the identified significant determinants of disease severity. For patients in the age range of 40 to 59 years and ≥ 60 years, the odds of having severe disease as compared with mild disease were 4.428 and 18.070 times than patients < 40 years, respectively. Similarly, the odds of having severe disease as compared with moderate disease among patients 40 to 59 years and ≥ 60 years were 4.871 and 18.906 times than patients < 40 years, respectively. 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 a natural diminishing of the body's defense mechanism and also the increased possibility of 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 unpublished study conducted

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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.

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 [15-21].

For patients with hypertension and diabetes, the odds of having moderate disease as compared with mild disease were 2.302 and 2.607 times compared to patients with no such illnesses, respectively. Similarly, the odds of having severe disease as compared with mild disease for hypertensive and diabetic patients were 1.966 and 3.926 times patients with no such illnesses, respectively. 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 [8,11,22,23].

In addition, the other important factors that determine disease severity were fever and headache. The odds of having moderate disease as compared with mild disease for patients with fever and headache were 6.115 and 2.695 times than patients with no such symptoms, respectively. The odds of having severe disease as compared with mild disease for patients with fever and headache were 13.218 and 4.816 times than patients with no such symptoms, respectively. Similarly, the odds of having severe disease as compared with mild disease for patients with fever and headache were 2.161 and 1.787 times compared to patients with no such symptoms, respectively. That means, having symptoms from COVID-19 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 determinants of disease severity. This implies that non-respiratory symptoms also might have a predictive value in disease categorization.

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CONCLUSION

The following factors were identified to be significant determinants of developing a more severe COVID-19 disease; being 40 years and above (especially 60 years and above), male sex, hypertension, diabetes, and having symptoms of fever and headache.

We recommend to aware the public to take extra precaution so that these vulnerable groups of patients can be protected from getting infected. It is also important to have a target group oriented screening for early detection of the disease for a better outcome. In addition, considering symptoms of fever and headache as indicators of a more severe disease category could be important.

Declaration

Ethics approval and consent to participate

The study was conducted after obtaining ethical clearance from St. Paul's Hospital Millennium Medical College Institutional Review Board. Written informed consent was obtained from the participants. 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.

Competing interests

The authors declare that they have no known competing interests

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