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Laboratory biomarkers of COVID-19 disease severity and outcome: Findings from a developing country

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Abstract

Aim

To identify laboratory biomarkers that predict disease severity and outcome among COVID-19 patients admitted to the Millennium COVID-19 Care Center in Ethiopia.

Methods

A retrospective cohort study was conducted among 429 COVID-19 patients who were on follow up from July to October 2020. Data was described using frequency tables. Robust Poisson regression model was used to identify predictors of COVID-19 severity where adjusted relative risk (ARR), P-value and 95 CI for ARR were used to test significance. Binary Logistic regression model was used to assess the presence of statistically significant association between the explanatory variables and COVID-19 outcome where adjusted odds ratio (AOR), P-value and 95%CI for AOR were used for testing significance.

Results

Among the 429 patients studied, 182 (42.4%) had Severe disease at admission and the rest 247 (57.6%) had Non-severe disease. Regarding disease outcome, 45 (10.5%) died and 384 (89.5%) were discharged alive. Age group (ARR = 1.779, 95%CI = 1.405–2.252, p-value <0.0001), Neutrophil to Lymphocyte ratio (NLR) (ARR = 4.769, 95%CI = 2.419–9.402 p-value <0.0001), Serum glutamic oxaloacetic transaminase (SGOT) (ARR = 1.358, 95%CI = 1.109–1.662 p-value = 0.003), Sodium (ARR = 1.321, 95%CI = 1.091–1.600 p-value = 0.004) and Potassium (ARR = 1.269, 95%CI = 1.059–1.521 p-value = 0.010) were found to be significant predictors of COVID-19 severity.

The following factors were significantly associated with COVID-19 outcome; age group (AOR = 2.767, 95%CI = 1.099–6.067, p-value = 0.031), white blood cell count (WBC) (AOR = 4.253, 95%CI = 1.918–9.429, p-value = 0.0001) and sodium level (AOR = 3.435, 95%CI = 1.439–8.198, p-value = 0.005).

Conclusions

Assessing and monitoring the laboratory markers of WBC, NLR, SGOT, sodium and potassium levels at the earliest stage of the disease could have a considerable role in halting disease progression and death.

Introduction

The growing threat due to the COVID-19 pandemic has caused numerous losses to the entire world. In Ethiopia as of October 2, 2020, a total of 120,630 cases were identified with 1, 864 deaths reported [1]. In the absence of a directed therapy and expanding vaccine service for the disease, identification of critical laboratory biomarkers for disease severity at early stage could help monitor and prevent disease progression towards severe form. To that aim studies to identify important clinical and laboratory biomarkers that can predict disease severity and outcome have been conducted. So far different clinical, laboratory and radiologic markers that can predict disease severity have been identified with varying results in the face of changing behavior of the disease and geographical disparity. Therefore, understanding predictors of disease severity and outcome are crucial to provide early preventive measures for a better outcome especially in economically developing country setup where intensive care setup might not match the increasing demand in the service.

Different laboratory markers are implicated as an indicator of disease severity, progression and outcome. Deranged cell counts, like anemia, polycythemia, leukopenia and leukocytosis with neutrophil predominance and decreased platelet count are found to be associated with severe disease and worse outcome in hospitalized patients [2–9]. Similarly raised liver enzymes and total bilirubin levels were identified in severe and critical patients [6,10–15].

Raised inflammatory response of the body as manifested by raised laboratory values of various interleukins and C-reactive proteins are also reported [4,7,16–18]. In addition, raised coagulation markers like fibrinogen and prothrombin time are identified in severe and critical patients [2,4].

Electrolyte imbalance in both directions, hypo- and hyper- levels were reported for sodium, potassium and calcium levels among patients with severe disease and worse outcome, hypothesized to result from the effect of the disease on the body system or the medication side effects [19–21].

There is limited study that assessed the role of laboratory markers in predicting disease severity and outcome in the African setup. Since the number of infected cases and mortality rate is reported to be lower than those reported in the non-African setup, understanding the disease predictors in our setup is crucial. Therefore, the aim of this study was to identify laboratory biomarkers that predict disease severity and outcome among COVID-19 patients admitted to the Millennium COVID-19 Care Center in Ethiopia from July to October 2020.

Materials and methods

Study setting, design and population

An institution based retrospective cohort study was conducted at Millennium COVID-19 Care Center (MCCC), a makeshift hospital in Addis Ababa, Ethiopia. The follow up was made from July to October, 2020. The source population was all cases of COVID-19 admitted at MCCC with a confirmed diagnosis of COVID-19 using RT-PCR, as reported by a laboratory

given mandate to test such patients by the Ethiopian Federal Ministry of Health and who were on follow up from July to October, 2020 [22].

All consecutively admitted Severe COVID-19 patients during the four months follow up period with complete baseline clinical and laboratory data and outcome data were included in the study. With these criteria, a total of 429 COVID-19 patients were included in the final analysis.

Eligibility criteria

All COVID-19 patients who were on treatment and follow up at the center from July to October, 2020 and with complete baseline clinical and laboratory data were included.

Operational definition

COVID-19 severity score: was determined based on the WHO classification as follows [23].

- **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 Disease:** These patients have developed complications. The following features can define severe illness.
  - Hypoxia: SPO2 $\leq$ 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

Data was extracted from patients' admission, follow up and discharge charts using a pretested electronic data abstraction tool that is adopted from the WHO CRF form. Data extractors were trained on the tool and appropriate infection prevention and control measures were followed. Data consistency and completeness was checked before an attempt was made to enter the code and analyze the data.

Data management and data analysis

Data was summarized using frequency tables and percentages.

A chi-square test/ Fischer's exact test were used to identify the presence of a statistically significant difference between COVID-19 severity and pre-existing co-morbid illness history and baseline laboratory biomarkers. A statistically significant difference was detected for variables with a P-value of $\leq$ 0.05.

To identify predictors of COVID-19 disease severity, Robust Poisson regression model was used. Variables significantly associated with disease severity at 25% level of significance in the univariate analysis were considered in the multivariable model. In the final model; adjusted RR, P-value and 95% CI for RR were used to test significance and interpretation of results. Variables with p-value $\leq$ 0.05 were considered as significant predictors of disease severity.

To assess the presence of statistically significant association between COVID-19 disease outcome (death) and the explanatory variables, Binary Logistic regression model was used. Univariate analysis was done to screen out independent variables to be used in the

multivariable Binary Logistic regression model at 25% level of significance. The adequacy of the final model was assessed using the Hosmer and Lemeshow goodness of fit test and the final model fitted the data well p-value = 0.876). For the Binary Logistic regression, 95% confidence interval for AOR was calculated and variables with p-value $\leq$ 0.05 were considered as statistically associated with disease outcome.

All analyses were performed using STATA software version 14 (College Station, TX).

Ethical considerations

The study was conducted after obtaining ethical clearance from St. Paul's Hospital Millennium Medical College Institutional Review Board (Ref No. pm23/23).

Written informed consent was obtained from the participants at the time of admission to take part in the research and to access their medical and laboratory recordings. The study had no risk/negative consequence on those who participated in the study. Medical record numbers were used for data collection and no personal identifiers were collected or used in the research report. Data was accessed from October 16 to November 5, 2020 and access to the collected information was limited to the principal investigator and confidentiality was maintained throughout the project.

Results

COVID-19 severity and disease outcome

Among the 429 patients studied, 182 (42.4%) had severe disease and the rest 247 (57.6%) had non-severe disease (15.6% mild and 42.0% moderate) at admission. Regarding disease outcome, 45 (10.5%) died and 384 (89.5%) were discharged alive.

Socio-demographic, comorbid illness and presenting symptoms

More than half of the participants were younger than 50 years (60.8%) and males (64.1%). Majority (95.3%) of the participants were from Addis Ababa, 11 (2.6%) were from different regions of Ethiopia and the rest 9 (2.1%) were individuals with a history of travel from outside Ethiopia. From the local cases, 321 (74.0%) acquired the infection through a community transmission, 92 (21.4%) had a history of contact with a confirmed case and the rest 7 (1.61%) had a history of contact with a traveler.

One hundred eighty eight (43.8%) had a history of one or more preexisting co-morbid illness. The majority had hypertension (25.2%), Type II diabetes mellitus (TIIDM) (19.8%), Asthma (6.1%) and cardiac disease (5.6%). Other co-morbid illness including chronic diseases of the lung, kidney, liver and neurology constituted less than 1% of the total cases. The commonest symptoms were cough (69.2%), followed by fatigue (29.1%) and fever (26.1%). (**Table 1**).

Baseline laboratory biomarkers

The complete blood count of the study participants showed that more than one-third (36.1%) had polycythemia and only 23 (5.4%) were anemic. Close to one-third had deranged white blood cell count (WBC), with 61 (14.2%) had leukopenic and 69 (16.1%) had leukocytosis. Majority had neutrophil predominant (66.2%) and lymphopenic cell count profile (71.3%). Only a quarter (26.8%) of patients had a normal Neutrophil to Lymphocyte ratio (NLR) of $\leq$ 3. Majority (85.1%) of the patients had a normal platelet count.

Three hundred forty seven (80.9%) of the patients had a raised urea value and 62 (14.5%) had raised creatinine. Raised liver enzymes level of Serum glutamic pyruvic transaminase

Table 1. Socio–demographic, co-morbid illness and presenting symptom related variables among COVID-19 patients (n = 429).

Variable	Total (%)	Variable	Total (%)
Age category (in years)		**Runny nose**	
< 19	17 (3.9)	No	400 (93.2)
20–29	68 (15.7)	Yes	29 (6.8)
30–39	105 (24.2)	**Chest pain**	
40–49	76 (17.5)	No	344 (80.2)
≥ 50	168 (39.2)	Yes	85 (19.8)
Sex		**Myalgia**	
Female	154 (35.9)	No	378 (88.1)
Male	275 (64.1)	Yes	51 (11.9)
Preexisting Co-morbid illness		**Arthralgia**	
No	241 (56.2)	No	369 (86.0)
Yes	188 (43.8)	Yes	60 (14.0)
Cardiac disease		**Fatigue**	
No	405 (94.4)	No	304 (70.9)
Yes	24 (5.6)	Yes	125 (29.1)
Hypertension		**Shortness of breath**	
No	321 (74.8)	No	281 (65.5)
Yes	108 (25.2)	Yes	148 (34.5)
Type II Diabetes Mellitus		**Headache**	
No	344 (80.2)	No	338 (78.8)
Yes	85 (19.8)	Yes	91 (21.2)
Asthma		**Abdominal pain**	
No	403 (93.3)	No	418 (97.4)
Yes	26 (6.1)	Yes	11 (2.6)
Fever		**Nausea/ vomiting**	
No	317 (73.9)	No	406 (94.6)
Yes	112 (26.1)	Yes	23 (5.4)
Cough		**Diarrhea**	
No	132 (30.8)	No	411 (95.8)
Yes	297 (69.2)	Yes	18 (4.2)
Sore throat			
No	352 (82.1)		
Yes	77 (17.9)		

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(SGPT), Serum glutamic oxaloacetic transaminase (SGOT) and Alkaline phosphatase (ALP) were recorded on 43.6%, 24.5% and 18.2% of the patients, respectively.

Abnormal serum levels of Sodium (Na) and Potassium (K) were observed in considerable proportion of patients. A higher proportion of deranged value was observed for hyponatremia and hyperkalemia which were observed in 63 (14.7%) and 127 (29.6%) of the patients, respectively. (Table 2).

Co-morbid illness and laboratory biomarker related variables and comparison between Non-severe Vs Severe COVID-19 patients

Based on the chi-square/ Fischer's exact test result, a statistically significant difference in COVID-19 disease severity was observed among the groups classified by the presence of

Table 2. Baseline laboratory biomarkers related variables among COVID-19 patients (n = 429).

Variables	Total (%)	Variables	Total (%)
Hematocrit (%)		**Urea** (mg/dl)	
<36	23 (5.4)	< 20	82 (19.1)
36–45	251 (58.5)	≥20	347 (80.9)
>45	155 (36.1)		
White Blood Cell (cells/ul)		**Creatinine** (mg/dl)	
<4.5	61 (14.2)	<0.6	48 (11.2)
4.5–11	299 (69.7)	0.6–1.1	319 (74.4)
>11	69 (16.1)	>1.1	62 (14.5)
Neutrophil %		**SGPT** (IU/L)	
<40	21 (4.9)	< 41	242 (56.4)
40–70	124 (28.9)	≥ 41	187 (43.6)
>70	284 (66.2)	**SGOT** (IU/L)	
Lymphocyte %		< 40	324 (75.5)
<20	306 (71.3)	≥ 40	105 (24.5)
20–50	119 (27.7)	**ALP** (IU/L)	
>50	4 (0.9)	< 100	351 (81.8)
NLR		≥ 100	78 (18.2)
≤ 3	115 (26.8)	**Na** (mequ/l)	
>3	314 (73.2)	<135	63 (14.7)
Platelet count (cells/ul)		135–145	349 (81.4)
<150	36 (8.4)	>145	17 (4.0)
15–450	365 (85.1)	**K** (mequ/l)	
>450	28 (6.5)	<3.5	17 (4.0)
		3.5–4.5	285 (66.4)
		>4.5	127 (29.6)

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cardiac disease, hypertension, type II diabetes mellitus and the laboratory biomarkers of NLR, platelet count, SGPT, SGOT, ALP, Na, K.

Accordingly, a significantly higher proportion of participants with chronic illnesses of cardiac, hypertension and diabetes presented with severe COVID-19 as compared with those with no such diseases. In addition, a significantly higher proportion of participates with raised NLR and deranged (decreased and/ or raised) values of platelet count, SGPT, SGOT, ALP, Na and K presented with severe COVID-19 as compared with participants with normal baseline values for these biomarkers. (Table 3).

Predictors of COVID-19 disease severity (Severe Vs Non-Severe)

Univariate analysis at 25% level of significance was conducted and age group, sex, hypertension, type II diabetes mellitus, fever, sore throat, myalgia, arthralgia, fatigue, headache, hematocrit (Hct), WBC, platelet count, NLR, urea, creatinine, SGPT, SGOT, ALP, Na and K were found to be predictors of COVID-19 disease severity.

On the multivariable Robust Poisson Regression, after adjusting for other covariates, age group, fever, fatigue, NLR, SGOT, Na and K were found to be significant predictors of COVID-19 disease severity at 5% level of significance.

After adjusting for other covariates, being 50 years and older increased risk of developing severe disease by 1.779 (ARR = 1.779, 95% CI = 1.405–2.252, p-value < 0.0001).

The presenting symptoms of patients particularly fever and fatigue were found to be significant predictors of disease severity showing a 1.252 (ARR = 1.252, 95% CI = 1.019–1.536,

Table 3. Co-morbid illness and laboratory biomarker related variables and comparison between Non-severe Vs Severe COVID-19 patients (n = 429).

Variable	COVID-19 Severity		p-value
	Non severe (n =)	Severe (n =)	
Cardiac			
No	241 (59.5)	164 (40.5)	**0.001***
Yes	6 (25.0)	18 (75.0)	
Hypertension			
No	200 (62.3)	121 (37.7)	**0.001***
Yes	47 (30.3)	108 (69.7)	
Type II Diabetes Mellitus			
No	213 (61.9)	131 (38.1)	< **0.0001***
Yes	34 (40.0)	51 (60.0)	
Asthma			
No	235 (58.3)	168 (41.7)	0.224
Yes	12 (46.2)	14 (53.8)	
Hematocrit			
<36%	13 (5.3)	10 (5.5)	0.992
36–45%	145 (58.7)	106 (58.2)	
>45%	89 (36.0)	66 (36.3)	
White blood cell count			
4.5–11 x10^3/ul	181 (60.5)	118 (39.5)	0.060
<4.5/>11/ul	66 (50.8)	64 (49.2)	
NLR			
≤3	107 (93.0)	8 (6.7)	< **0.0001***
>3	140 (44.6)	174 (55.4)	
Platelet Count			
150–450 x10^3/ul	222 (60.8)	143 (39.2)	**0.001***
<150/>450/ul	25 (39.1)	39 (60.9)	
Urea			
<20 mg/dl	195 (56.2)	152 (43.8)	0.234
≥20 mg/dl	52 (63.4)	30 (36.6)	
Creatinine			
0.6–1.1 mg/dl	192 (60.2)	127 (39.8)	0.062
<0.6/>1.1 mg/dl	55 (50.0)	55 (50.0)	
SGPT			
<41 IU/L	158 (65.3)	84 (34.7)	< **0.0001***
≥41 IU/L	89 (47.6)	98 (52.4)	
SGOT			
<40 IU/L	222 (68.5)	102 (31.5)	< **0.0001***
≥40 IU/L	25 (23.8)	80 (76.2)	
ALP			
<100 IU/L	217 (61.8)	134 (38.2)	< **0.0001***
≥100 IU/L	30 (38.5)	48 (61.5)	
Na			
135–145 mequ/l	226 (64.8)	123 (35.2)	< **0.0001***
<135/>145 mequ/l	21 (26.2)	59 (73.8)	
K			
3.5–4.5 mequ/l	182 (63.9)	103 (36.1)	< **0.0001***
<3.5/>4.5 mequ/l	65 (45.1)	79 (54.9)	

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p-value = 0.032) and 1.414 (ARR = 1.414, 95% CI = 1.153–1.732 p-value = 0.001) times increased risk of having severe disease as compared to patients with no such symptoms, respectively.

NLR of greater than 3 was associated with a 4.769 times increased risk of developing severe disease as compared with those with a value of 3 and lower (ARR = 4.769, 95% CI = 2.419, 9.402 p-value <0.0001).

Having a raised SGOT of 41 and above increased the risk of having severe disease by 35.8% compared to those with value of a normal range (ARR = 1.358, 95% CI = 1.109, 1.662 p-value = 0.003).

The risk of developing severe disease among patients with deranged values of Na and K level (both hypo- and hyper- levels) was 1.321 (ARR = 1.321, 95% CI = 1.091, 1.600 p-value = 0.004) and 1.269 (ARR = 1.269, 95% CI = 1.059, 1.521 p-value = 0.010) times that of patients with a normal values of Na and K, respectively. (Table 4).

Predictors of COVID-19 disease outcome (Death Vs Recovery)

Crude analysis of each independent variable with disease outcome was run at 25% level of significance. From univariate analysis; age group, sex, hypertension, TIIDM, sore throat, chest pain, myalgia, arthralgia, fatigue, respiratory rate, Hct, WBC, platelet count, urea, creatinine, SGPT, SGOT, ALP, Na and K were found to be significantly associated with COVID-19 disease outcome.

However; only age group, WBC and Na level were found to be significantly associated with disease outcome in the multivariable binary logistic regression model at 5% level of significance.

Table 4. Results of the final multivariable robust poisson regression model among COVID-19 patients (n = 429).

Variable	CRR (95% CI)	ARR (95% CI)	p-value
Age group (≥ 50 Vs < 50 Years)	2.544 (2.024, 3.197)	**1.779 (1.405, 2.252)**	**<0.0001***
Sex (Male Vs Female)	1.363 (1.059, 1.753)	1.204 (0.983, 1.474)	0.072
Hypertension (Yes Vs No)	1.498 (1.206, 1.862)	1.117 (0.914, 1.364)	0.277
Type II Diabetes Mellitus (Yes Vs No)	1.576 (1.264, 1.963)	0.989 (0.789, 1.236)	0.916
Fever (Yes Vs No)	1.572 (1.270, 1.947)	**1.252 (1.019, 1.536)**	**0.032***
Sorethroat (Yes Vs No)	1.206 (0.931, 1.563)	1.169 (0.929, 1.470)	0.184
Myalgia (Yes Vs No)	1.581 (1.237, 2.021)	0.877 (0.695, 1.106)	0.268
Arthralgia (Yes Vs No)	1.732 (1.389, 2.160)	1.213 (0.948, 1.551)	0.124
Fatigue (Yes Vs No)	2.342 (1.985, 2.979)	**1.414 (1.153, 1.732)**	**0.001***
Headache (Yes Vs No)	1.330 (1.052, 1.683)	1.085 (0.879, 1.338)	0.448
Hematocrit (>45 Vs ≤45%)	0.766 (0.597, 0.981)	0.889 (0.728, 1.088)	0.254
White blood cell count (<4.5/>11/ul Vs 4.5–11 x10^3/ul)	1.247 (0.997, 1.561)	0.958 (0.796, 1.152)	0.646
NLR (>3 Vs ≤3)	7.966 (4.049, 15.669)	**4.769 (2.419, 9.402)**	**<0.0001***
Platelet Count (<150/>450/ul Vs 150–450 x10^3/ul)	1.555 (1.230, 1.966)	1.238 (0.984, 1.557)	0.069
Urea (≥20 Vs <20 mg/dl)	1.197 (0.879, 1.631)	1.122 (0.852, 1.477)	0.413
Creatinine (<0.6/>1.1 Vs 0.6–1.1 mg/dl mg/dl)	1.256 (0.997, 1.582)	1.009 (0.809, 1.258)	0.936
SGPT (≥41 Vs <41 IU/L)	1.509 (1.211, 1.882)	1.056 (0.873, 1.277)	0.576
SGOT (≥40 Vs <40 IU/L)	2.420 (1.994, 2.936)	**1.358 (1.109, 1.662)**	**0.003***
ALP (≥100 Vs <100 IU/L)	1.612 (1.292, 2.009)	1.021 (0.846, 1.232)	0.828
Na (<135/>145 mequ/l Vs 135–145 mequ/l)	2.092 (1.724, 2.539)	**1.321 (1.091, 1.600)**	**0.004***
K (<3.5/>4.5 mequ/l Vs 3.5–4.5 mequ/l)	1.518 (1.225, 1.881)	**1.269 (1.059, 1.521)**	**0.010***

Note: CRR, Crude Risk ratio; ARR, Adjusted Risk ratio; CI, Confidence interval

*statistically significant.

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Table 5. Result of Multivariable Binary logistic regression model among COVID-19 patients (n = 429).

Variable	COR (95% CI)	AOR (95% CI)	p-value
Age category (≥ 50 Vs < 50 Years)	5.072 (2.536, 10.144)	**2.767 (1.099, 6.967)**	**0.031***
Sex (Male Vs Female)	1.834 (0.901, 3.733)	2.076 (0.841, 5.121)	0.113
Hypertension (Yes Vs No)	2.691 (1.427, 5.074)	1.567 (0.640, 3.836)	0.325
Type II Diabetes Mellitus (Yes Vs No)	3.926 (2.059, 7.488)	1.774 (0.718, 4.385)	0.214
Sorethroat (Yes Vs No)	0.416 (0.144, 1.197)	0.467 (0.122, 1.786)	0.266
Chestpain (Yes Vs No)	1.991 (1.007, 3.936)	1.104 (0.418, 2.917)	0.841
Myalgia (Yes Vs No)	1.715 (0.750, 3.922)	0.911 (0.255, 3.253)	0.886
Arthralgia (Yes Vs No)	1.909 (0.890, 4.093)	2.441 (0.739, 8.069)	0.143
Fatigue (Yes Vs No)	2.610 (1.395, 4.883)	0.965 (0.376, 2.476)	0.940
Respiratory rate (> 20 Vs ≤20/min)	2.665 (1.283, 5.537)	2.145 (0.853, 5.396)	0.105
Hematocrit (>45 Vs ≤45%)	0.539 (0.265, 1.097)	0.549 (0.229, 1.319)	0.180
White blood cell count (<4.5/>11/ul Vs 4.5–11 x10^3/ul)	4.554 (2.392, 8.669)	**4.253 (1.918, 9.429)**	**0.0001***
Platelet Count (<150/>450/ul Vs 150–450 x10^3/ul)	1.746 (0.817, 3.731)	0.732 (0.254, 2.111)	0.563
Urea (≥20 Vs <20 mg/dl)	2.613 (0.909, 7.514)	1.916 (0.566, 6.480)	0.296
Creatinine (<0.6/>1.1 Vs 0.6–1.1 mg/dl mg/dl)	3.217 (1.712, 6.048)	1.956 (0.829, 4.614)	0.126
SGPT (≥41 Vs <41 IU/L)	2.892 (1.506, 5.552)	2.013 (0.840, 4.822)	0.116
SGOT (≥40 Vs <40 IU/L)	5.283 (2.782, 10.032)	1.534 (0.644, 3.655)	0.334
ALP (≥100 Vs <100 IU/L)	4.025 (2.094, 7.737)	1.825 (0.779, 4.273)	0.166
Na (<135/>145 meu/l Vs 135–145 mequ/l)	7.477 (3.889, 14.375)	**3.435 (1.439, 8.198)**	**0.005***
K (<3.5/>4.5 mequ/l Vs 3.5–4.5 mequ/l)	2.054 (1.102, 3.829)	1.299 (0.583, 2.897)	0.522

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

*statistically significant.

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Accordingly, after adjusting for other covariates, the odds of dying among patients who were 50 years and older was 2.767 times compared with those less than 50 years of age (AOR = 2.767, 95% CI = 1.099, 6.067, p-value = 0.031).

The laboratory markers that are found to be significant determinants of disease outcome were WBC count and Na level. After being adjusted for other factors, having deranged laboratory markers (both lower and raised values) of WBC count and Na level were associated with 4.253 times (AOR = 4.253, 95% CI = 1.918, 9.429, p-value = 0.0001) and 3.435 times (AOR = 3.435, 95% CI = 1.439, 8.198, p-value = 0.005) higher odds of dying compared to those with normal values for these markers. (Table 5).

Discussion

In this study, we assessed the effect of clinical and laboratory markers on COVID-19 disease severity and outcome among 429 COVID-19 patients who were admitted to Millennium COVID-19 Care Center in Ethiopia from July to October 2020. Timely identification of biomarkers of COVID-19 disease severity and death would help to provide targeted intervention and patient management. Among the 429 patients studied, 247 (57.6%) had Non-severe disease (15.6% mild and 42.0% moderate) and the rest 182 (42.4%) had Severe disease at admission. Regarding disease outcome, 45 (10.5%) died and 384 (89.5%) were discharged alive. On the multivariable robust Poisson regression model at 5% level of significance, age group, NLR, SGOT, Sodium and Potassium were found to be significant predictors of COVID-19 disease severity.

Accordingly, after adjusting for other covariates, being 50 years and older was found to be associated with a 1.779 times increased risk of developing severe disease. Age is implicated to be associated with severe disease and outcome in different studies conducted in Chine, United states and Europe [24–27]. Similar finding is also reported from studies conducted in our country [28,29]. The reasons behind could be the increased possibility of weaker immune defense mechanism and co-morbid illnesses making older individuals prone to different illnesses with severe progression and worst outcome.

Symptoms of fever and fatigue were found to be significant predictors of disease severity showing a 1.252 and 1.414 times increased risk of having severe disease as compared to patients with no such symptoms, respectively. Having symptomatic disease, other than symptoms used in disease classification, in general is reported to delay disease recovery and also found to be associated with more severe disease category in another study conducted at the same Center (MCCC) [29,30].

NLR of greater than three is associated with a 4.769 times increased risk of developing severe disease as compared with those with a value of three and less. As an indicator of the body's systemic inflammation, a raised level of this inflammatory biomarker above three indicates the body's stress. With more stress, as in severe and critical patient states, the level increases to even higher level. Therefore, this biomarker is an indirect indication of the body's stress level due to the severity of the disease. This is also similar with findings from studies conducted in China and also systematic review findings where NLR was found to an important predictor of disease severity and outcome [3,5–8].

Having a raised SGOT of 41 and above was associated with a 1.358 times increased risk of having severe disease as compared with those with value of a normal range. Different mechanisms are pointed to the possible effect of the SARS-CoV-2 Virus on liver; the virus could directly affect the hepatocytes or the liver could get injured indirectly through enhanced inflammatory response due to the raised immune markers and drug toxicity that are meant to treat or halt the progression of the disease resulting in liver damage and thereby an increase in liver enzymes [31]. Raised in liver enzymes associated with more severe disease category is also reported in other studies [10–15].

The risk of developing severe disease among patients with deranged values of Na and K level (both hypo- and hyper- levels) was 1.321 and 1.269 times than patients with a normal values of Na and K, respectively. Electrolyte imbalances in any disease condition can result from fluid losses from the body through different routes, renal damage and effect of medication that is administered to treat the disease and/or concomitant illnesses. It is also implicated to be due to the decreased activity of angiotensin-converting enzyme 2 which is claimed to be a receptor for the severe acute respiratory syndrome coronavirus 2. This electrolyte imbalance will in turn affect the different body organ system function that could compromise the body's appropriate response to the stress caused by the disease thereby leading to more severe disease, complication and death. This is also demonstrated in other studies, where both increased and decreased levels of Na and K are found to be associated with severe disease states [19–21].

On the assessment of factors associated with disease outcome, age group, WBC and Na level were found to be significantly associated with disease outcome on multivariable analysis at 5% level of significance.

Accordingly, after adjusting for other covariates, the odds of dying among patients who were 50 years and older was 2.767 times compared with those less than 50 years of age. Similar to the above finding where age is associated with more severe disease condition, it is also implicated to be associated with severe disease outcome.

The laboratory markers that are found to be significant determinants of disease outcome were white blood cell count and sodium level.

After being adjusted for other factors, having deranged laboratory markers (both lower and raised values) of white blood cell count was associated with a 4.253 times higher odds of dying compared to those with normal values. Both leukopenia and leukocytosis are found to be associated with severe COVID-19. Having decreased white cell count increases the potential to develop serious infection and expansion of an already existing pathogen thereby leading to the development of critical disease stage in any infection. Similarly, although a raised white cell count is an indication of a strong immune system responding to external threat, it also implies that the body is under a lot of stress from the pathogenic organism.

Similarly, having deranged laboratory markers (both lower and raised values) of Na level was associated with a 3.435 times higher odds of dying compared to those with normal values for this marker. As discussed above, hyponatremia and hypernatremia that can result from different underlying disease conditions or from the medications given to treat the disease are found to be associated with severe disease and worse outcomes as demonstrated by different studies as well [20,21].

Conclusions

In this study we have assessed laboratory markers that can predict disease severity and outcome. Accordingly, NLR of above three, raised SGOT and deranged Na and K levels (both hypo- and hyper-states) were found to be significant predictors of developing severe COVID-19 disease. In addition, deranged values of WBC and Na levels were significantly associated with worse outcome of the disease.

Therefore, assessing and monitoring these laboratory markers at the earliest stage of the disease could have a considerable input in halting disease progression and death.

Supporting information

S1 Data.
(SAV)

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