

Prognostic Value of C-Reactive Protein in SARS-CoV-2 Infection: A Simplified Biomarker of COVID-19 Severity in Northern Ethiopia

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Purpose: To evaluate the role of C-reactive protein (CRP) in predicting severe COVID-19 patients.

Methods: A prospective observational cohort study was conducted from July 15 to October 28, 2020, at Kuyha COVID-19 isolation and treatment center hospital, Mekelle City, Northern Ethiopia. A total of 670 blood samples were collected serially. SARS-CoV-2 infection was confirmed by RT-PCR from nasopharyngeal swabs and CRP concentration was determined using Cobas Integra 400 Plus (Roche). Data were analyzed using STATA version 14. P-value <0.05 was considered statistically significant.

Results: Overall, COVID-19 patients had significantly elevated CRP at baseline when compared to PCR-negative controls [median 11.1 (IQR: 2.0–127.8) mg/L vs 0.9 (IQR: 0.5–1.9) mg/L; $p=0.0004$]. Those with severe COVID-19 clinical presentation had significantly higher median CRP levels compared to those with non-severe cases [166.1 (IQR: 48.6–332.5) mg/L vs 2.4 (IQR: 1.2–7.6) mg/L; $p<0.0001$]. Moreover, COVID-19 patients exhibited higher median CRP levels at baseline [58 (IQR: 2.0–127.8) mg/L] that decreased significantly to 2.4 (IQR: 1.4–3.9) mg/L after 40 days after symptom onset ($p<0.0001$). Performance of CRP levels determined using ROC analysis distinguished severe from non-severe COVID-19 patients, with an AUC value of 0.83 (95% CI: 0.73–0.91; $p=0.001$; 77.4% sensitivity and 89.4% specificity). In multivariable analysis, CRP levels above 30 mg/L were significantly associated with an increased risk of developing severe COVID-19 for those who have higher ages and comorbidities (ARR 3.99, 95% CI: 1.35–11.82; $p=0.013$).

Conclusion: CRP was found to be an independent determinant factor for severe COVID-19 patients. Therefore, CRP levels in COVID-19 patients in African settings may provide a simple, prompt, and inexpensive assessment of the severity status at baseline and monitoring of treatment outcomes.

Keywords: CRP, COVID-19, SARS-CoV-2, biomarker

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiology of the coronavirus disease 2019 (COVID-19), has resulted in an unprecedented global pandemic with a total of over 670 million cases and over 6.8 million deaths globally as of March 30, 2023.¹ COVID-19 presents with a multitude of clinical features, spanning from asymptomatic or mild to severe or critical form.^{2,3} Severe and critical COVID-19 is associated with acute respiratory distress syndrome, requiring

hospitalization, supplemental oxygen, and/or mechanical ventilation. Risk factors associated with the severe disease include older age and the presence of comorbidities, such as hypertension, diabetes, chronic obstructive lung diseases, and chronic kidney diseases.^{4–8}

In the Sub-Saharan Africa (SSA) context, similar risk factors have also been reported.^{9,10} The whole mark characteristics of the severe form of COVID-19 have been linked to the overproduction of several pro-inflammatory cytokines, leading to cytokine storms.^{11,12} When compared to mild/moderate COVID-19 cases, patients with severe disease have markedly increased levels of pro-inflammatory cytokines, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-17, tumor necrosis factor (TNF)- α and interferon (IFN)- γ .^{4,13–17} In addition to cytokine deregulation, cytokine storm in severe COVID-19 is also associated with coagulopathy.^{18–20}

C-reactive protein (CRP) belongs among the surrogate biomarkers of cytokine storm.²¹ CRP is an acute phase reactant produced by the liver that serves as an early marker of infection and inflammation and is largely produced in response to IL-6.²² Emerging evidence indicates that IL-6 plays a pivotal role in the pathogenesis of cytokine storm associated with severe COVID-19,^{23–26} and CRP levels may act as a reliable surrogate for IL-6 bioactivity.^{21,22} Cumulative reports have demonstrated that levels of CRP increased during severe COVID-19.^{27–29}

Few mild/ moderate COVID-19 patients develop a severe disease level. Thus, it is crucial to early identify and put into treatment this group of patients to reduce and improve their disease severity. Some studies showed that the degree of severity and mortality of patients with COVID-19 is due to an altered level of some blood markers; CRP has been found as an important biomarker in determining changes in patients with severe COVID-19.^{28,30,31} Moreover, CRP could be used effectively as a routine blood parameter to determine the prognosis and diagnosis of COVID-19.^{32,33}

Measurement of the various cytokine levels associated with cytokine storms in the setting of SSA, particularly in Ethiopia is not realistic given the challenges faced concerning suboptimal laboratory infrastructure. However, recent improvements in the determination of low concentration by the high-sensitivity CRP (hs-CRP) methods are developed, which are rapid, easy, inexpensive, and readily available in the majority of SSA healthcare facilities.³⁴ Unfortunately, there is no data available on the role of CRP as a determinant prognostic marker for COVID-19 severity status in northern Ethiopia and there is a paucity of data on the kinetics of CRP levels among Ethiopian COVID-19 patients. In this study, therefore, we aimed to assess the prognostic value of CRP levels in the various categories of COVID-19 patients as stratified by severity status.

Methods

Study Design, Period, and Population

This study is part of the ongoing Profile-Cov study, a prospective observational cohort study being undertaken in Ethiopia (Clinicaltrials.gov: NCT04473365). Consecutive patients (n=78) with confirmed real-time polymerase chain reaction (RT-PCR) test results for SARS-CoV-2 and RT-PCR negative controls (n = 50) were enrolled. They were prospectively recruited from Kuyha Hospital COVID-19 Isolation and Treatment Center, College of Health Science, Mekelle University, Northern Ethiopia, between July 15 and October 28, 2020.

Data Collection

Socio-demographic and clinical data were collected using standardized Case Record Forms (CRFs) adapted from the International Severe Acute Respiratory and Emerging Infection Consortium's (ISARIC) CRFs for emerging severe acute respiratory infections.³⁵ The patient's clinical status was stratified following WHO criteria as asymptomatic, mild/moderate, severe (with dyspnea, respiratory rate ≥ 30 breaths per minute, O₂ saturation $\leq 93\%$, lung infiltrates $\geq 50\%$ of the lung fields within 24–48 hours), and critical (with respiratory failure, septic shock, and/or multiple organ failure).³⁶ For this study, asymptomatic and mild/moderate cases were considered non-severe cases and both severe and critical patients were considered severe cases. The date of symptom onset was determined for symptomatic cases. For asymptomatic patients, however, we added 6 days (median time between symptom onset and date of PCR testing among symptomatic cases) to post-PCR testing.

Sample Collection Process

For the confirmation of SARS-CoV-2 infection, nasopharyngeal swabs were collected and put in virus transport media and then sent immediately to the Ayder Central Laboratory of the University Hospital for diagnosis. For the analysis of the kinetics of CRP levels, 3–5 mL of whole blood was collected using an EDTA tube, and a total of 620 blood samples were drawn longitudinally from the 78 COVID-19 patients. Whenever possible, samples were drawn every 3 days until day 30 post-admission.

The samples were stored at room temperature for at least 30 min and then centrifuged at 3500 g for 5 min at room temperature. After separation of the plasma, the specimen was promptly separated into 2 aliquots of 3 mL in Nalgene cryovials and stored at -80°C Ayder Central Laboratory of the University hospital. Specimens were immediately transported to EPHI Clinical Chemistry Laboratory for further analysis. In addition to the above, for determining specificity, RT-PCR negative controls ($n = 50$) were obtained during the COVID-19 pandemic (August and September 2020) from individuals not suspected of SARS-CoV-2 infection.

Laboratory Assays

SARS-CoV-2 infection was confirmed by RT-PCR on samples obtained from nasopharyngeal swabs. The swabs collected were then put onto virus transport media and sent immediately to the central laboratory. RT-PCR for the detection of SARS-CoV-2 infection was based on the LightMix® Modular SARS and Wuhan CoV E-gene kit (TIB Molbiol, Berlin, Germany), as described previously.⁹ CRP concentration was determined by immune-turbidimetric (reagent CRPHS Ref. 04628918190) assay analyzed using the Cobas Integra 400® Plus (Roche Diagnostics GmbH, Mannheim, Germany) at the EPHI National Reference Laboratory for Clinical Chemistry, as per the manufacturer's instructions described previously.³⁴

Quality Control

Data quality was maintained using standardized Case Record Forms (CRFs) adapted from the International Severe Acute Respiratory and Emerging Infection Consortium's (ISARIC) CRFs for emerging severe acute respiratory infections. The reliability of the findings was guaranteed by implementing quality control measures throughout the whole process of laboratory work. Two internal quality control materials at two different levels (PreciControl ClinChem Multi 1 ref. 05947626190, CRP T Control N Ref. 20766321322) were also analyzed during all analytical series. The analytical characteristics of CRP are as follows: the limit of the blank, the limit of detection, and the limit of quantitation were 0.1, 0.2, and 0.3 mg/L, respectively. Over the study period, the assay had a 1.23% coefficient of variation (CV) with a 10.6 mg/L mean (CRP T Control) and a 4.30% CV with a 7.9 mg/L mean for Preci Control Clin Chem Multi 1. The National Reference Laboratory for Clinical Chemistry participated in the external quality assurance program (One World Accuracy), which is accredited by the Ethiopia National Accreditation Office.

Statistical Analysis

Data were entered into electronic medical records and checked for completeness and analyzed using STATA (Statistical package v. 14.0, StataCorp, Texas, USA).

Baseline characteristics for continuous variables were expressed as the median with interquartile range (IQR), and for categorical variables as proportions. Whereas categorical variables were compared using χ^2 test or Fisher's exact test, continuous variables were compared by Mann–Whitney U, or Kruskal–Wallis tests, as appropriate. Normality of distribution of variables was ascertained by running Wilk test of normality, before analysis by Mann–Whitney U, or Kruskal–Wallis tests. The area under the receiver operating characteristic (ROC) curve (AUC) was analyzed to assess the diagnostic value of CRP by comparing PCR-confirmed COVID-19 patients with PCR-negative controls as well as to predict COVID-19 severity. The maximum potential effectiveness of CRP as a biomarker was calculated using the Youden index. Poisson regression analysis was used to determine risk factors associated with developing severe COVID-19. $p < 0.05$ were considered statistically significant.

Results

Characteristics of Study Participants

A total of 78 COVID-19 patients who tested positive on RT-PCR for SARS-CoV-2 were included in the study. The majority of study participants (76.3%) were male (Table 1). The median age of the cohort was 34 (IQR: 28–50) years, with 53.0% being in the age range of 24 to 44 years. Whereas 49 (62.8%) patients were asymptomatic or mild/moderate cases (non-severe COVID-19), the remaining 29 (37.2%) patients presented with severe disease. Although there was no difference in gender distribution between non-severe and severe groups, COVID-19 patients presenting with severe clinical status were older [median age 50 years (IQR:

Table 1 Baseline Socio-Demographic and Clinical Characteristics of COVID-19 Patients

Characteristic	All Patients N=78	Non-Severe Patients (Asymptomatic and Mild/Moderate) N= 49	Severe Patients (Severe and Critical) N= 29	p- value
Socio-demographic features				
Gender (male), N (%)	60 (76.9)	39 (79.6)	21 (72.4)	0.467
Age in years [median (IQR)]	34 (28–50)	30 (26–37)	50 (36–66)	<0.00001
Age group [years, N (%)]				
< 60	66 (84.6)	49 (100.0)	17 (58.6)	<0.0001
≥ 60	12 (15.4)	0 (0.0)	12 (41.1)	
Clinical symptoms and signs				
Fever, N (%)	23 (29.5)	7 (14.3)	16 (55.2)	<0.0001
Dyspnoea, N (%)	30 (38.5)	5 (10.2)	25 (86.2)	<0.0001
Cough (any type, N (%))	36 (46.2)	12 (24.5)	24 (82.8)	<0.0001
Non-productive cough	26 (33.3)	5 (10.2)	21 (72.4)	<0.0001
Productive cough	10 (12.8)	7 (14.9)	3 (10.3)	
Chest pain, N (%)	8 (10.3)	1 (2.0)	7 (24.0)	0.002
Sore throat, N (%)	6 (7.7)	1 (2.0)	5 (17.2)	0.015
Headache, N (%)	21 (26.9)	9 (18.4)	12 (41.4)	0.027
Nasal congestion, N (%)	5 (6.4)	4 (8.2)	1 (3.5)	0.411
Anosmia and/or dysgeusia, N (%)	3 (3.9)	2 (4.1)	1 (3.5)	0.888
Diarrhoea, N (%)	1 (1.3)	0 (0.0)	1 (3.5)	0.191
Myalgia, N (%)	9 (11.5)	4 (8.2)	5 (17.2)	0.225
Temperature (median °C, IQR)	36.6 (36.0–37.0)	36.4 (36.0–36.8)	36.7 (36.3–37.0)	0.029
Systolic blood pressure (median mmHg, IQR)	115 (105–120)	112 (105–120)	124 (110–130)	0.022
Diastolic blood pressure (median mmHg, IQR)	74 (70–80)	74 (70–78)	76 (70–83)	0.216
Respiratory rate (median breaths/minute, IQR)	22 (19–28)	20 (18–22)	29 (28–31)	<0.00001
Heart rate (median beats/minute, IQR)	83 (76–102)	76 (73–83)	105 (98–112)	<0.00001
Laboratory markers				
Lymphocyte, $\times 10^9/L$	1.6 (0.9–1.9)	1.8 (1.6–2.3)	1.4 (0.5–1.7)	0.020
Hematocrit, %	42.9 (34.5–46.1)	45.6 (42.2–47.6)	42.3 (28.6–45.3)	0.018
Platelet count, $\times 10^9/L$	234 (174–328)	232 (168–247)	237 (174–375)	0.468
Alanine aminotransferase concentration, U/L	49 (39–70)	51 (49–275)	41 (36–70)	0.139
Creatinine concentration, mg/dL	0.60 (0.38–0.75)	0.53 (0.20–0.63)	0.70 (0.40–0.90)	0.130
Comorbidities				
Comorbidity (at least 1)	21 (26.9)	2 (4.1)	19 (65.5)	<0.0001
Non-communicable diseases (NCDs)				
Comorbidities	18 (23.1)	2 (4.1)	16 (55.2)	<0.0001
Diabetes	9 (11.5)	2 (4.1)	7 (24.1)	0.007
Hypertension	7 (9.0)	0 (0.0)	7 (24.1)	<0.0001
Outcomes				
Admission to ICU	6 (7.7)	0 (0.0)	6 (20.7)	0.001
Supplemental oxygen	29 (37.2)	0 (0.0)	29 (100.0)	<0.0001
Invasive mechanical ventilation	2 (2.6)	0 (0.0)	2 (6.9)	0.063
Death	2 (2.6)	0 (0.0)	2 (6.9)	0.063

Notes: Data are expressed as n (%) or median (IQR). p values are from the χ^2 test, or Fisher's Exact test (for categorical variables), and Mann–Whitney U, or Kruskal–Wallis tests (for continuous variables), as appropriate.

Abbreviations: IQR, Interquartile range, N, Number.

36–66) vs 30 years (IQR: 26–37); $p<0.00001$]. Patients with severe disease symptoms when compared to non-severe cases were more dyspneic (86.2% vs 10.2%), had more cough (82.8% vs 24.5%), fever (55.2% vs 14.3%), headache (41.4% vs 18.4%), chest pain (24.0% vs 2.0%), sore throat (17.2% vs 2.0%), and myalgia ((17.2% vs 2.0%). Nasal congestion, diarrhea, and loss of smell and/or taste were not frequent in both patient groups. Patients with severe COVID-19 were significantly more likely to be tachypneic when compared to those with non-severe disease [median 29 (IQR: 28–31) vs 20 (IQR: 18–22) breaths/minute; $p<0.00001$]. Likewise, patients with severe disease were significantly more likely to be tachycardic when compared to those with non-severe cases [median 105 (IQR: 98–112) vs 76 (IQR: 73–83) beats/minute; $p<0.00001$]. Lymphocyte count was also significantly lower among severe COVID-19 patients compared to those with non-severe clinical manifestations. Comorbidities were significantly higher among severe COVID-19 cases when compared to non-severe (65.5% vs 4.1%; $p<0.0001$). In addition, COVID-19 patients with severe disease have more NCDs than non-severe cases (55.2% vs 4.1%; $p<0.0001$). Moreover, all severe cases of COVID-19 patients were admitted to the intensive care unit and received supplemental oxygen therapy, or mechanical ventilation (Table 1).

Kinetics of CRP Levels Among COVID-19 Patients

As shown in Figure 1A, PCR-confirmed COVID-19 patients had significantly elevated CRP at baseline when compared to PCR-negative controls [median 11.1 (IQR: 2.0–127.8) mg/L vs 0.9 (IQR: 0.5–1.9) mg/L; $p=0.0004$]. Moreover, COVID-19 patients with non-severe clinical presentation had higher levels of CRP compared to PCR-negative controls [median 2.4 (IQR: 1.2–7.6) mg/L vs 0.9 (IQR: 0.5–1.9) mg/L; $p=0.0007$]. Those with severe COVID-19 clinical

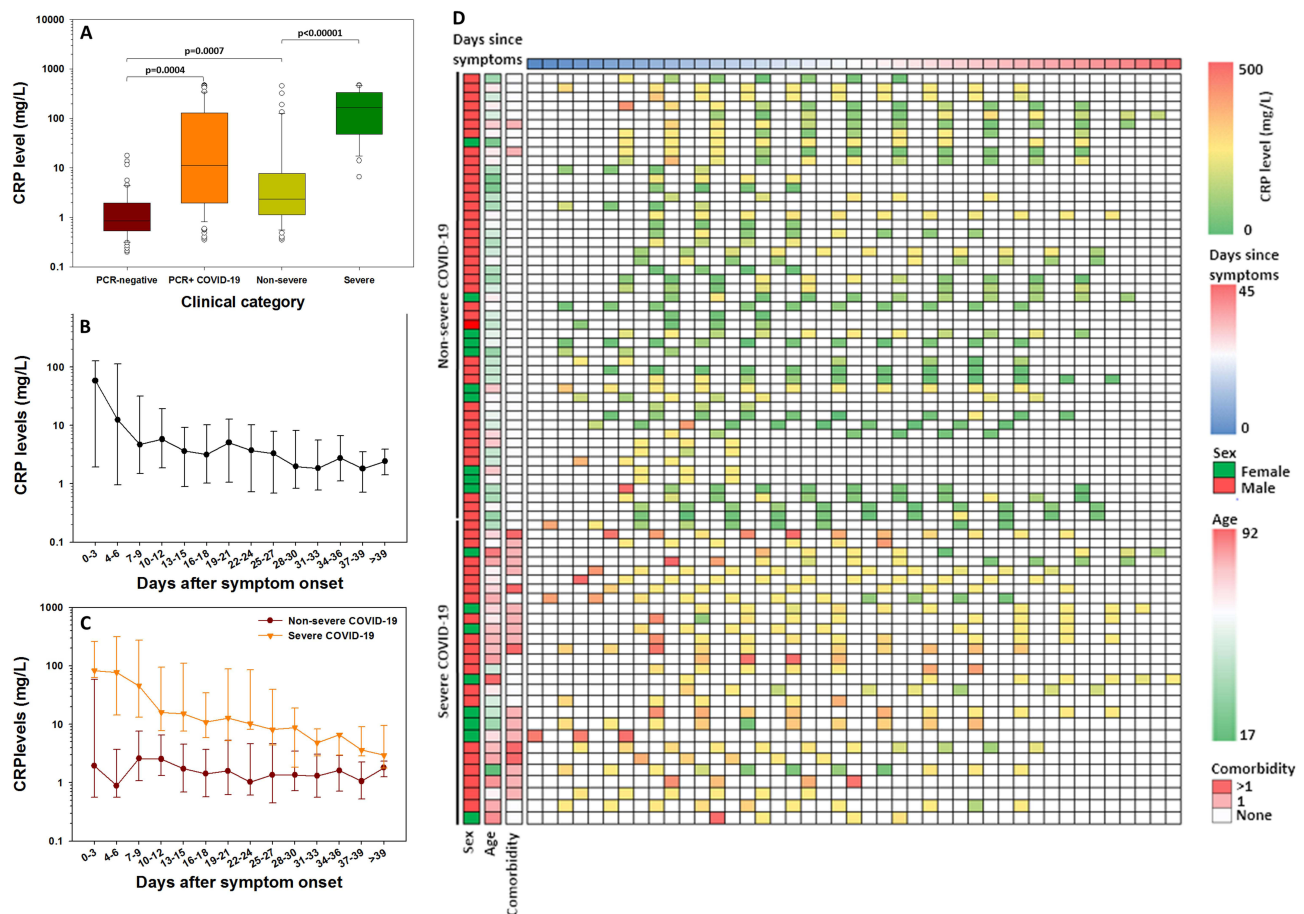


Figure 1 CRP levels among PCR-negative controls, PCR-confirmed COVID-19 patients, and COVID-19 patients stratified by severity status (A); kinetics of CRP levels following symptom onset and during hospitalization (B), and stratified by severity status (C). Data are median and 25% to 75% interquartile ranges. Heat-map plot analysis of CRP levels of COVID-19 patients clustered according to severity status (D).

presentation had significantly higher median CRP levels compared to those with non-severe cases [166.1 (IQR: 48.6–332.5) mg/L vs 2.4 (IQR: 1.2–7.6) mg/L; $p < 0.00001$].

The Kinetics of CRP levels is shown in Figure 1B–D. Overall, COVID-19 patients exhibited higher median CRP levels at baseline [58 (IQR: 2.0–127.8) mg/L] that decreased significantly to 4.7 (IQR: 1.5–31.5) mg/L after day 7 to 10 after the onset of symptom(s) ($p < 0.0001$), and to 2.4 (IQR: 1.4–3.9) mg/L after 40 days after symptom onset ($p < 0.0001$). Nonetheless, severe cases had significantly elevated median CRP levels at admission [83.1 (IQR: 62.6–258.7) mg/L], maintained at > 30 mg/L up until day 7 post symptom onset, and decreased slowly during hospitalization significantly to a median of 3.0 (IQR: 1.8–9.6) mg/L after 40 days of symptom onset ($p < 0.0001$ for trend) (Figure 1C). Non-severe COVID-19 patients exhibited low-level CRP levels throughout the disease. Notably, persistently elevated levels of CRP were exhibited among those with comorbidities and higher age groups (Figure 1D). In addition, the proportion of COVID-19 patients with elevated CRP levels is higher in severe cases when compared to non-severe patients considering CRP levels at cut-off values of 3.0, 8.0, 30.0, and 50.0 mg/L (Figure 2). In the severe group, over 40% of patients had persistently elevated CRP levels up until day 30 following symptom onset (Figure 2). Six patients with severe COVID-19 admitted to the ICU (of whom two died) exhibited persistently elevated CRP levels throughout the disease (Figure 3).

To assess the diagnostic value of CRP, we initially determined the AUC and compared the CRP levels in PCR-confirmed COVID-19 patients and PCR-negative controls. For this comparison, we considered CRP level > 1.0 mg/L as an increased CRP level, based on our previous results obtained by determining CRP level in the general population in Ethiopia. Of note, PCR-negative controls in our study had a median CRP level of 0.9 (IQR: 0.5–1.9) mg/L, which is similar to the median CRP level of 0.8 mg/L obtained from the population-based study in Ethiopia. ROC analysis of CRP levels distinguished PCR-confirmed COVID-19 patients from the ones with PCR-negative non-COVID-19 individuals, with an AUC value of 0.77 (95% CI: 0.68–0.84; $p = 0.001$; 76.7% sensitivity and 76.3% specificity) (Figure 4A). In addition, we further determined the performance of CRP levels in distinguishing severe from non-severe COVID-19. Here, we considered a cut-off of 30 mg/L. Thus, ROC analysis distinguished severe from non-severe COVID-19 patients, with an AUC value of 0.83 (95% CI: 0.73–0.91; $p = 0.001$; 77.4% sensitivity and 84% specificity) (Figure 4B).

After adjusting for age and the presence of comorbidities, the multivariate Poisson regression analysis showed that CRP levels ≥ 8 mg/L were significantly associated with an increased risk of developing severe COVID-19 (AOR 3.99 (95% CI: 1.35–11.82), $p = 0.013$) (Table 2).

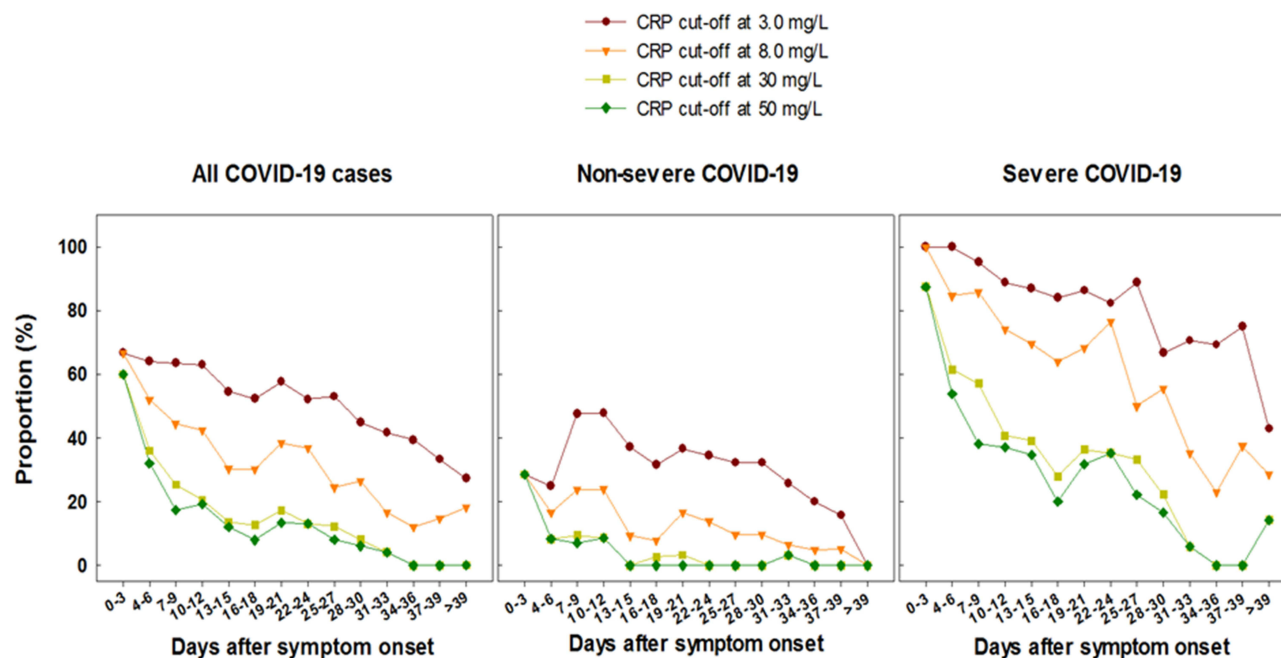


Figure 2 Kinetics of CRP levels in all, non-severe and severe COVID-19 patients at different CRP cut-off values.

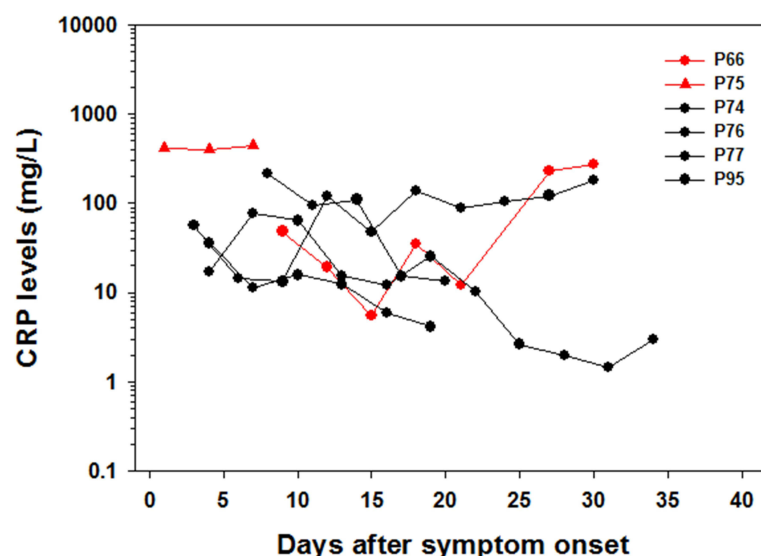


Figure 3 Kinetics of CRP levels in six COVID-19 patients admitted to the ICU. The red lines represent two patients who died during follow-up. Black lines denote 4 patients admitted to the ICU, but who survived.

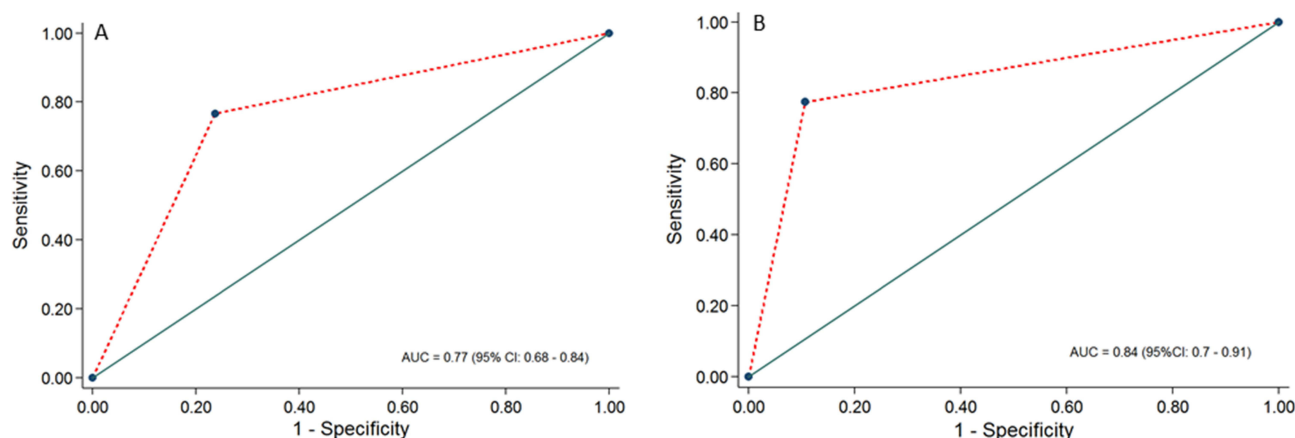


Figure 4 AUCs analysis of CRP between PCR-confirmed COVID-19 patients and PCR-negative controls (A), and between severe and non-severe COVID-19 patients (B).

Discussion

Several reports have demonstrated that inflammatory cytokines, such as IL-6 serve as a surrogate risk biomarker for severe COVID-19.^{13,14,16,18–20} However, determining such biomarkers is not easy in a setting of SSA like Ethiopia. Thus, simple, readily available, and inexpensive biomarkers for assessing the degree of severity of COVID-19 patients in Ethiopia are urgently needed. CRP is such a biomarker that can easily and promptly be determined to assess the severity status of COVID-19 patients for immediate assessment in Ethiopia, including monitoring of any therapeutic intervention.

In this study, we determined CRP levels in SARS-CoV-2 PCR-negative individuals as well as COVID-19 patients from Ethiopia with a different spectrum of clinical severity. Our results extend findings from earlier reports that CRP level in COVID-19 patients is in general elevated when compared to healthy controls,²⁵ as well as it is significantly increased in severe than in non-severe COVID-19 patients.^{23–29} Among the symptomatic cohort participants, the most common symptoms noted at presentation were dyspnea, had more cough, fever, headache, chest pain, sore throat, and myalgia. This was similar to the findings of studies from Nigeria³⁷ and South Africa.³⁸ We noted that the risk of developing severe COVID-19 in patients with baseline 8 mg/L or above is increased significantly by around 4-fold when compared to those below 8 mg/L. In addition, we observed a significant elevation of CRP in those with comorbidities, particularly those with NCDs were more prevalent than communicable diseases, indicating a more intense induction of hyperinflammation. This is in line with previous studies of Fachri et al,³⁹ and Chen et al,²⁷ who showed CRP were increased in COVID-19 patients co-infected by NCDs.

Table 2 Factors Associated with the Risk of Developing Severe COVID-19 Disease

Characteristic	Crude OR (95% CI)	p- value	Adjusted OR (95% CI)	p- value
Sex				
Male	2.56 (0.85–6.07)	0.096	1.33 (0.35–2.07)	0.212
Female			1.00	
Age				
≥ 60	3.84 (0.89–9.16)	0.066	1.92 (0.33–4.16)	0.129
< 60			1.00	
Comorbidities				
Comorbidity (at least 1)	5.23 (1.22–15.32)	0.021	2.24 (0.94–8.32)	0.068
Non-communicable diseases (NCDs)				
Comorbidities	1.46 (0.91–2.39)	0.75	1.02 (0.57–1.83)	0.31
Diabetes	3.83 (0.8–11.04)	0.99	1.012 (0.2–3.32)	0.099
Hypertension	6.07 (0.91–16.43)	0.87	3.21 (0.31–8.43)	0.32
CRP				
CRP at baseline (≥ 8 mg/L)	7.014 (4.10–21.61)		3.99 (1.35–11.82)	0.013*
CRP at cohort (<8 mg/L)			1.00	

Note: 1.00=Reference, *Significant at P value<0.05.

Abbreviations: CRP, C-reactive protein, CI, confidence interval, OR, Odds ratio, Adjusted OR, for age and co-morbidities.

To the best of our knowledge, this is the first study to analyze the longitudinal profile of CRP among hospitalized COVID-19 patients with different categories of clinical spectrum in the setting of SSA. We demonstrated that the CRP levels are persistently elevated in COVID-19 patients that require ICU admission, including those who died. Our findings are in line with those reported previously from other non-African settings.^{24–29} Hence, special attention should be taken to identify such cases to provide necessary intervention and to reduce morbidity and mortality.

Analysis of the receiver operating characteristic curve was found to be an independent distinguishing factor for severe COVID-19 patients with a cut-off of 30 mg/L from non-severe cases. This is lower than previous reports by Stringer et al, CRP > 40 mg/L,⁴⁰ and Sadeghi et al, CRP >64.75 mg/L.⁴¹ This indicates that the performance of CRP in predicting severe COVID-19 patients is better than the previous studies with an AUC value of 0.83 (95% CI: 0.73–0.91; p=0.001; 77.4% sensitivity and 89.4% specificity). In addition to assessing CRP level as a risk biomarker for categorizing COVID-19 patient severity, determining longitudinal CRP levels is relevant in assessing response to therapeutic intervention. Indeed, treatment of severe COVID-19 patients with an anti-IL-6 monoclonal antibody, tocilizumab, showed a significant reduction in CRP level, from 75.1 mg/L at baseline to 2.7 mg/L at day 5 post tocilizumab therapy.⁴²

The present study showed the success of CRP in distinguishing PCR-confirmed COVID-19 patients from these PCR-negative non-COVID-19 individuals with an AUC value of 77%, 76.7% sensitivity, and 76.3% specificity. Huyut et al have noted the diagnostic performances of CRP with an AUC value of 73.4% as an effective predictive biomarker of COVID-19 mortality.³¹ Numerous other studies have shown that CRP and other routine immunological and hematological parameters could be the most effective diagnostic markers of COVID-19 patients.^{32,43,44}

The strength of the study includes a prospective study design with longitudinal follow-up of CRP level allowed us to monitor the severity of COVID-19 during follow-up. Nonetheless, the small sample size and lack of comparative assessment of other biomarkers are considered shortcomings of the study.

Conclusion

We have shown that CRP levels are significantly elevated among COVID-19 patients compared to PCR-negative controls and that CRP levels were significantly elevated in severe than in non-severe COVID-19 patients. CRP was found to be an independent distinguishing factor for severe COVID-19 patients with a cut-off of 30 mg/L from non-severe cases. In addition, persistently elevated CRP levels were associated with the risk of developing severe COVID-19 including the requirement for admission to the ICU and death. Determining CRP levels in COVID-19 patients in the SSA setting may provide a simple, prompt, and inexpensive assessment of the severity status at baseline and monitoring of treatment outcomes.

Data Sharing Statement

The data used to support the findings of this study are included in the article.

Ethics Approval and Consent to Participate

Participants enrolled provided written consent to participate in the Profile-CoV study. The study protocol was reviewed and approved by the Health Research Ethics Review Committee of Mekelle University College of Health Sciences (#ERC 1769/2020) and the Ethiopian Public Health Institute (#EPHI 6.13/814). The study did not use any personal patient information, and all data were kept confidential following the revised Declaration of Helsinki.

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Disclosure

The authors have no competing interests to declare

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