Original article

Do CRP levels predict severity in COVID-19 hospitalized Egyptian patients?

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A R T I C L E   I N F O

A B S T R A C T

Background: Coronavirus disease 2019 (COVID-19) is a rapidly spreading virus with a wide range of clinical manifestations. To manage treatment programs and promptly assess patient severity, prognostic factors must be identified early. **Objectives:** The purpose of this study was to investigate if there was a link between the severity of COVID-19 and the C-reactive protein (CRP) level on admission. **Methods:** On admission clinical and laboratory data from 323 patients with laboratory-confirmed COVID-19 were gathered from an Isolation Hospital records from April 10, 2020 to July 30, 2020. CRP was determined in all participants using an automated analyzer and a commercially available latex-enhanced immuno-turbidimetric assay. **Results:** The most prevalent presenting symptom was fever (39.3%), followed by cough (38.4%). Coronavirus disease 2019 severity and ICU admission were both predicted by high CRP levels ($p<0.001$). C-reactive protein levels were also greater in those who had more chest discomfort, as indicated by CT chest abnormalities ($p<0.001$). **Conclusion:** Serum CRP is a simple and effective prognosticator for early prediction of COVID-19 severity.

Introduction

Since its discovery in Wuhan, China, in December 2018, the Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has progressed to the point of becoming a global pandemic [1]. It has affected innumerable countries all over the world [2-4]. It has a wide range of clinical symptoms, ranging from asymptomatic to severe pneumonia with multisystemic failure and patient mortality [5]. Nearly 20% of COVID-19 patients possibly acquire life-threatening complications that involve septic shock, coagulation dysfunction, and multiple organ failure [6]. According to previous several previous studies, COVID-19 progression may be aided by an abnormal immune-inflammatory response and cytokine storm [7,8].

C-reactive protein (CRP) is a pentameric acute-phase reactant produced by the liver, and its level rises in response to the action of cytokines like

interleukin-6 (IL-6) during an inflammatory/infectious process [9,10]. C-reactive protein elevations, alone or in combination with other inflammatory biomarkers, can indicate bacterial or viral infections [11]. C-reactive protein has been studied for its predictive usefulness in a variety of illnesses, including hepatitis C, dengue fever, and malaria [12-14]. Its rise during infections indicates the extent of tissue involvement, allowing for the diagnosis of perplexing consequences [15].

The inflammatory response is important in the progression of COVID-19 [11]. As a result, finding a simple and effective prognosticator is vital for identifying and treating potentially critical individuals, with the goal of lowering mortality rates [15].

This study aims to investigate whether CRP can predict the severity of COVID-19 disease.

Materials and Methods

Subjects and Setting

This cross-sectional study included all COVID-19 patients (n=323) admitted to El-Obour Ain Shams University Specialized Isolation Hospital in the period from April 10, 2020, to July 30, 2020. Patients who were pregnant or had missing data were eliminated from the study.

COVID-19 infection was confirmed in all patients using reverse transcription polymerase chain reaction (RT-PCR). According to the Ain Shams University Hospitals Consensus Statement on Management of Adult COVID-19 Patients, the patients were stratified into three groups based on the severity of their disease.

• Mild cases: Asymptomatic with abnormal laboratory findings or symptomatic with no COVID-19 pneumonia on chest CT.

• Moderate cases: Symptomatic with non-severe pneumonia (e.g., fever, cough, dyspnea), as well as abnormal laboratory findings.

• Severe cases: Chest CT findings of COVID-19 pneumonia and clinical evidence of significant pneumonia (e.g., respiratory rate > 30 breaths/min; severe respiratory distress; or saturation of peripheral oxygen (SpO_2) 93 percent on room air).

Of all included patients, sociodemographic data, complete medical history, the existence of co-morbid conditions, and laboratory data were obtained from hospital medical records. Complete blood picture with differential count, serum D-dimer, ferritin, liver function tests, and kidney

function tests were among the tests performed routinely for isolated patients on admission.

C-reactive protein serum level was determined in all participants using an automated analyzer and a commercially available latex-enhanced immuno-turbidimetric assay (BIOLIs 24i Tokyo Boeki, Japan). The typical level was around 5 mg/L.

Computerized tomography (CT) protocol and grading

Chest CT scans were performed with a single inspiratory phase in one commercial multi-detector CT scanner (Activion™ 16 Multislice CT System, Toshiba, Japan.). Patients were asked to hold their breath to decrease the motion induced artifacts. Computerized tomography images were taken by the protocol of tube voltage, 100–120 kVp; effective tube current, 110–250 mAs, detector collimation, 0.625 mm; slice thickness,1 mm; slice interval, 0.8 mm. Typical CT findings ground-glass opacity (GGO); consolidation; crazy-paving; cavitation; mediastinal lymphadenopathy; pleural effusion. The radiological severity was determined utilizing the method developed by Michael Chung et al, the number of involved lung lobes and the lesion distribution were also noted to assess the radiological severity [16].

Each of the lung lobes was assessed using a scoring system:

• 0= no involvement to a lobe (0%)

• 1= minimal involvement to a lobe (1–25%)

• 2= mild involvement to a lobe (26–50%)

• 3= moderate involvement to a lobe (51–75%)

• 4= severe involvement to a lobe (76–100%).

A total score was obtained summing the cores of five lobe scores (range of possible scores, 0–20).

And the severity of lung involved on CT scan was classified on a 4-point ordinal scale:

• grade 0 score of 0 (No abnormality presents on CT)

• grade one score of 1–5

• grade two score of 6–15

• grade three score of 16–20

Statistical analysis

The collected data were processed and coded before being analyzed using the IBM SPSS program (Statistical Package for Social Sciences) for Windows Version 20.0. Qualitative data were

presented using frequencies and related percentages. Quantitative data were presented using means and standard deviations (SD) or medians and interquartile ranges (IQR). An independent samples t-test or Mann–Whitney U test was used to compare the difference in parametric variables between two independent means of two groups. ANOVA or Kruskal-Wallis test was performed to compare quantitative variables among three categories. The chi-squared or Fisher's exact test was performed for qualitative variable analysis. The strength of association between two variables was tested by Pearson (parametric) and Spearman (non-parametric) correlation tests. The predictive performance of CRP was assessed by the receiver operating characteristic (ROC) curve. The statistical methods were verified, assuming a significance level of $p<0.05$.

Results

The participants in this study (n=323) ranged in age from 10 to 85 years old, with a mean age of 46.6 (SD 16.3) years. Males made up 171 (52.9%) of the total, while females made up 152 (47.1%). Only 21 people (6.5%) were smokers.

Fever (39.3%) then cough (38.4%) were the most common presenting symptoms. **Table 1** summarizes the presenting symptoms of all the patients.

C-reactive protein levels were measured for 323 patients with a mean value of 42.26 mg/L (SD 68.90) and ranging between 1 and 710 mg/L. While the median (IQR) value of serum ferritin was 130 ng/ml (28 – 654) and it ranged from 0.5 to 4460 ng/ml. Besides, the median (IQR) value of D-dimer was 200 ng/ml (18 – 667) and it ranged from 0.2 – 9.848 ng/ml.

The need for ICU admission was reported in nearly one-fifth of the patients (total number 62; 19.2%), meanwhile the rest of the patients (total number 261; 80.8%) received treatment at the hospital ward.

Patients' severity at the time of hospital admission was: 181 (56%) mild, 102 (31.6%) moderate, and 40 (12.4%) severe.

Table 2 shows the levels of lymphocytes count, neutrophil to lymphocyte ratio (NLR), D-dimer concentration, and serum ferritin among mild, moderate severe cases. There was a statistically significant difference between mild and severe cases regarding lymphocytes count ($p=0.021$). Severe

cases displayed a statistically significantly lower lymphocytes count. On the other hand, NLR was statistically significantly higher in severe cases than in mild or moderate cases ($p=0.002$). Moreover, as the degree of severity increased there was a corresponding significant increase in the levels of D-dimer concentration and serum Ferritin ($p<0.001$).

Table 3 compares CRP levels with ICU admission, levels of severity and the findings of CT chest. High CRP levels were predictive of higher COVID-19 severity and ICU admission. Patients showing a mean ($\pm$SD) CRP of 60.17 $\pm$ 92.83 mg/L were patients regarded as moderately severe cases. Besides, the mean ($\pm$SD) CRP level of 91.29 $\pm$ 81.96 mg/L was present in severe cases of COVID-19, where patients having a mean ($\pm$SD) CRP of 101.97 $\pm$ 107.56 mg/L displayed the need for ICU admission. On the other hand, mild cases of COVID-19 had a mean ($\pm$SD) CRP equivalent to 20.53 (SD 2.48) mg/L.

Likewise, CRP levels were higher in patients with more chest affection as denoted by the CT chest findings. Patients having grade 2 severity score in their CT scans had a mean ($\pm$SD) CRP equivalent to 67.47 $\pm$ 90.04 mg/L. In addition, those having grade 3 severity score showed a mean ($\pm$SD) CRP equivalent to 89.40 $\pm$ 68.32 mg/L. However, patients having free CT scans (grade 0 severity) or just grade 1 severity score CT findings had a mean ($\pm$SD) CRP of 18.66 + 25.59 mg/L and 8.93 $\pm$ 4.32 mg/L.

Table 4 shows the correlations between CRP levels and age, different CBC parameters, serum Ferritin and D-dimer levels. C-reactive protein levels were statistically significantly positively correlated to age, serum Ferritin concentration, D-dimers levels, total leucocytes count, neutrophil concentration, monocyte's concentration. In addition, high CRP levels were significantly correlated to higher levels of NLR. Nevertheless, there was a statistically significant negative correlation between CRP levels and lymphocytes concentration.

Figure 1 shows that the cut-off point of differentiation between mild to moderate cases and severe cases was 141 mg/L and the area under the curve was 0.738. CRP displayed a negative predictive value of 92.4% and specificity of 95.39%.

Table 1. Presenting symptoms of admitted COVID-19 patients at Ain Shams University Hospitals (n=323).

Symptom	Number	Percentage
Asymptomatic	36	11.1
Fever	127	39.3
Sore throat	1	0.3
Cough	124	38.4
Dyspnea	18	5.6
Diarrhea	6	19
Melena	1	0.3

Table 2. The levels of lymphocytes count, neutrophil to lymphocyte ratio, D-dimer concentration, and serum ferritin among mild, moderate severe cases.

		Mild	Moderate	Severe	Test value	*p*-value
		No. = 181	No. = 102	No. = 40		
Lymphocytes (×10³/μL)	**Median (IQR)**	1.59 (1.2 – 2.12)	1.3 (0.7 – 1.94)	1.3 (0.75 – 1.9)	7.756	0.021
	Range	0.1 – 12.36	0 – 4.96	0.28 – 5.40		
Neutrophil/lymphocyte ratio	**Median (IQR)**	2.33 (1.31 – 4)	3.22 (1.59 – 7.76)	4.59 (2.1 – 11.26)	12.770	0.002
	Range	0 – 32.31	0.45 – 36.67	0.56 – 96.80		
Ferritin (ng/mL)	**Median (IQR)**	92 (13.75 – 199)	500 (128 – 914)	814.5 (130 – 1200)	54.516	<0.001
	Range	0.5 – 4460	0.5 – 2990	12 – 2734		
D-dimer (ng/ml)	**Median (IQR)**	149 (4 – 256)	300 (111 – 880)	779 (179 – 1900)	29.994	<0.001
	Range	0.2 – 7006	0.6 – 9848	79 – 5698		

Table 3. Comparison between CRP levels (mg/L) according to ICU admission and severity at hospital admission.

Variable		CRP levels (Mean ± SD)	*p*-value
ICU admission	**Yes**	101.97 ± 107.56	**<0.001**
	No	25.67 ± 40.32	
Severity		**Mild** 20.53 ± 2.48	**<0.001**
		Moderate 60.17 ± 92.83	
		Severe 91.29 ± 81.96	
CT Chest	**Grade 0**	18.66 ± 25.59	**<0.001**
	Grade 1	8.93 ± 4.32	
	Grade 2	67.47 ± 90.04	
	Grade 3	89.40 ± 68.32	

Table 4. Correlations between CRP levels and age, different CBC parameters, serum ferritin and D-dimer levels

	CRP	
	r	**_p_-value**
Ferritin	0.462	<0.001
D-dimer	0.164	0.018
Age	0.288	<0.001
Hemoglobin	-0.102	0.084
Platelets	0.007	0.902
Lymphocytes	-0.178	0.003
Monocytes	0.125	0.037
Neutrophils	0.260	<0.001
Platelets/ Lymphocytes ratio	0.169	0.005
Neutrophils/ Lymphocytes ratio	0.298	<0.001
Monocytes/Lymphocytes ratio	0.199	0.001
Total leucocytic count	0.218	<0.001

Figure 1. ROC curve of CRP level as a predictor of COVID-19 severity between mild to moderate and severe cases.
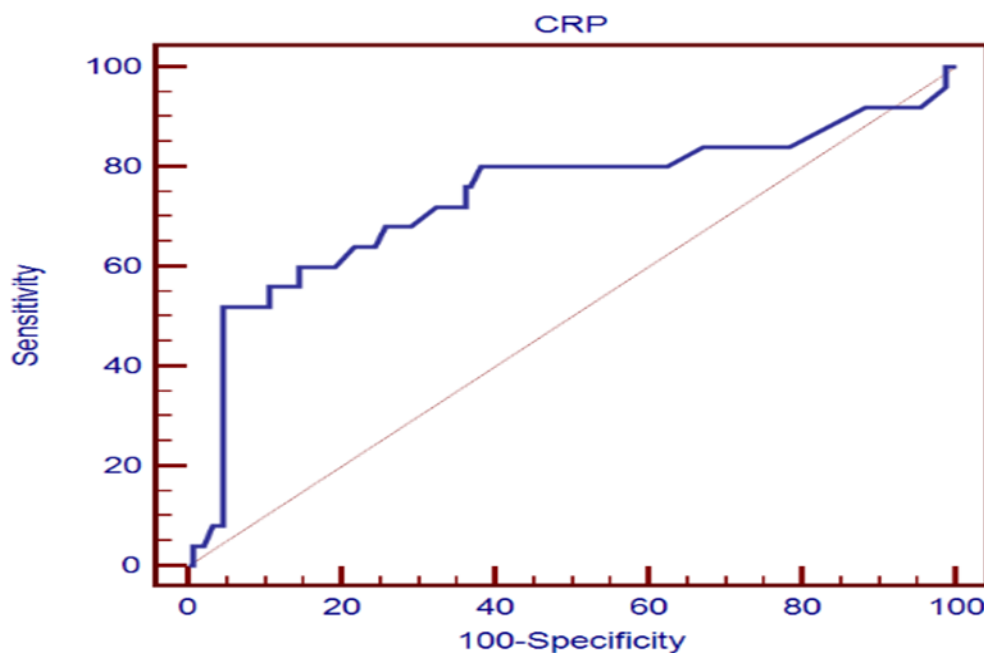
Parameter	AUC	Cut-off point	Sensitivity	Specificity	PPV	NPV
CRP (mg/L)	0.738	>141	52.0%	95.39%	65.0%	92.4%

AUC; area under the curve, PPV; positive predictive value, NPV; negative predictive value.

Discussion

The clinical course of COVID-19 pandemic is regarded as being highly variable. Though most of the patients suffered only from mild symptoms, an important percentage of patients suffered from severe symptoms due to viral-induced hyperinflammation up to respiratory failure with a need for mechanical ventilation [17,18]. Because the progression of these patients' clinical conditions is difficult to predict, early identification of prognostic markers is critical for regulating treatment programs and determining the severity of patients' conditions [19].

In the current study, the male to female ratio was 1.12:1. Only 21 (6.5%) were smokers. Fever then cough were the most common presenting symptoms.

In a similar investigation, **Li and colleagues** examined the epidemiologic data of the first 425 confirmed COVID-19 patients in Wuhan. Their findings found that males were the majority of patients, with fever being the most common symptom, followed by cough [20]. **Guan and Zhong** also found that fever (87.9%) and cough (67.7%) were the most frequent presentations in a study conducted on 1099 COVID-19 cases [21]. Moreover, **Zhao and collaborators** reported that fever and cough were the most common presenting manifestations [22].

In immunoinflammatory responses, sex hormones play a critical role. During an illness, male and female sex hormones have opposing effects on the immunological response. Female sex hormone enhances both innate and adaptive immune responses, resulting in faster pathogen clearance and greater infection endurance. Testosterone, on the other hand, has a negative impact on the immune system. This explains why COVID-19 patients are overwhelmingly male [23].

Several published epidemiological studies supported the current results showing low prevalence of smoking among confirmed cases [21,24,25]. Though smoking exerts several harmful effects, it also has beneficial effects via modulation of the immune system and its anti-inflammatory impact. Nicotine prevents acute lung injury via inhibition of production of proinflammatory cytokines release thus smoking may result in reduction of severe COVID-19 [26].

A cytokine cascade is the chief factor in COVID-19 induced hyperinflammation together with multiorgan failure [18]. The levels of certain blood markers (IL-1b, IL-6, IL-12, ferritin) in decrepit patients during cytokine storm are elevated [27]. IL-6 is a cytokine having multifunction which is accountable for induction of liver cells to enhance synthesis and production of CRP [28-30]. Since, the assessment of CRP level is a part of admission work up in isolation hospitals, we investigated the link between CRP levels at the time of admission and the severity of COVID-19, as well as the risk of ICU admission.

This study revealed that high CRP levels were predictive of more severe COVID-19 infection and ICU admission. These results are in parallel with **Shang and collaborators** who studied the clinical records of 443 patients divided into non-severe patients (n = 304) and severe patients (n = 139). They ascertained that NLR, CRP, and platelets can efficiently evaluate the severity of COVID-19 [31]. **Liu and collaborators** also found a significant correlation between CRP and the severity of COVID-19 and suggested its use in predicting disease severity as independent -risk factor [11].

Correspondingly, this research drew our attention to the fact that the correlation between CRP and the extent of chest affection via CT. C-reactive protein levels correlated with the extent of chest affection as denoted by the CT chest findings. **Wang** stated that CRP levels can trigger complement and phagocytosis, eliminating pathogens from the body. C-reactive protein is used to diagnose and assess severe pulmonary infectious illnesses [32].

In a recent systematic review, CRP was used with a binary threshold; proposed values to predict inpatient mortality ranged from ≥10 mg/L to ≥76 mg/L. Also, CRP has been examined in a trichotomized model with two thresholds at ≥40 mg/L and ≥100 mg/L. A lower cut-off of ≥20.44 mg/L was used as a threshold for related lung injury, and >32.5 mg/L was found to offer 80% predictive power for a person needing mechanical ventilation [33].

Chen and collaborators performed an observational retrospective study on 76 cases infected by SARS-CoV-2 [34]. They disclosed a positive correlation between serum CRP level and pulmonary affection on CT chest, regardless of age and lymphocytic count. On comparing mild CT findings, the CRP concentration in significantly rose

by11.47 mg/L p<0.05. Moreover, the serum CRP increased significantly by 23.40 mg/L in the moderate and severe CT affection. Their results agree with the present results.

Pathology reports of diseased patients have revealed occurrence of micro thrombosis in pulmonary vessels [35]. This is due to occurrence of hemostatic dysfunction resulting in hypercoagulable state in COVID-19 patients [36,37]. Proinflammatory cytokines as well as cellular damage result in elevation of serum ferritin level either via induction of ferritin synthesis or leakage of intracellular ferritin. Several studies declared that high serum D-dimer, and ferritin levels were linked to bad prognosis in COVID-19 [35-40]. The present study discerned that severe cases had significant higher levels of D-dimer and serum ferritin. Moreover, high serum CRP levels were significantly associated with high levels of D-dimer and serum ferritin.

Neutrophil to lymphocyte ratio is a simple, quick index of prognosis of systemic inflammation various conditions including ulcerative colitis, malignancies, acute coronary syndrome, and community acquired pneumonia [41-44]. Lots of studies stated that severe cases of COVID-19 are inclined to have greater values of NLR and declared that it is an independent risk factor for mortality in hospitalized patients with COVID-19 [41-45]. In this study, severe cases had higher values of NLR than mild and moderate cases. Besides high CRP levels were significantly associated with high levels of NLR.

Jimeno and collaborators conducted a study to evaluate the accuracy of the prognostic value of NLR and the concluded that it was highly specific and sensitive [46]. In addition, **Chan AS et al.** performed a study to ascertain the correlation of NLR to the severity of COVID-19 and they declared that NLR is an independent marker of severity in COVID-19 [47].

Ferritin and D-dimer levels at admission were increased in the progressive cohort, compared to mild (i.e., stable). C-reactive protein is downstream to several immune pathways, suggesting that CRP levels are dynamic early in hospital admission and precede respiratory deterioration [48].

Initial CRP and ferritin values reported modest elevations in progressive disease comparison with mild disease. However, maximum CRP levels were highly correlated and suggested

that CRP values were dynamic during COVID-19 illness [48].

Given the current study's findings that CRP has a favorable link with severity indicators, and a statistically significant increase in values with disease severity and lung ailment, it appears to be a simple and effective prognosticator. In the current study using the ROC curve analysis to detect the predictive value of CRP for COVID-19 severity, the best cut-off value of CRP for differentiation between mild to moderate cases and severe cases was 141 mg/L and the area under the curve was 0.738. At this point, CRP displayed a negative predictive value of 92.4% and a specificity of 95.39%.

Conclusion

Serum CRP is a simple and effective prognosticator that can identify COVID-19 patients who are at risk to develop severe disease and allow for early intervention.

Ethical consideration

Ethical approval for the current study protocol was obtained from Ain Shams University Faculty of Medicine Research Ethics Committee (REC) FWA 00017585.

Conflict of interest

No conflict of interest.

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