

# Do CRP Levels Predict Severity in COVID-19 Hospitalized Egyptian Patients?

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## Abstract

Background Coronavirus disease 2019 (COVID-19), has affected countless countries all over the world with rapidly increasing case fatality reports and a highly variable clinical course. Since the evolution of the clinical condition of these patients is difficult to forecast, early identification of prognostic indicators is an essential foundation to regulate treatment plans and promptly identify the severity of patients' conditions. Aim: To assess the correlation between CRP level on admission with the severity of the COVID-19, the risk for ICU admission and the findings in CT chest Method A retrospective cohort study where the clinical data of 276 patients with laboratory-confirmed COVID-19 infection were collected from El Obour Ain Shams University Specialized Hospital for Isolation records on admission from April 10, 2020 till July 30, 2020. Results Fever was the most common presenting symptom (total number 135; 41.7%), followed by cough (total number 133; 41.2%). High CRP levels were predictive of higher COVID-19 severity and ICU admission ( $p=0.000$ ). Likewise, CRP levels were higher in patients with more chest affection as denoted by the CT chest findings ( $p=0.000$ ). Conclusion Serum CRP is a simple and effective prognosticator which casts light on potentially critical patients. Consequently, it can be used to reduce the mortality of patients. Keywords: COVID-19, Hospital, CRP, ICU, severity.

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## Background

Coronavirus disease 2019 (COVID-19), has affected countless countries all over the world with rapidly increasing case fatality reports and a highly variable clinical course. Since the evolution of the clinical condition of these patients is difficult to forecast, early identification of prognostic indicators is an essential foundation to regulate treatment plans and promptly identify the severity of patients' conditions.

**Aim:** To assess the correlation between CRP level on admission with the severity of the COVID-19, the risk for ICU admission and the findings in CT chest

## Method

A retrospective cohort study where the clinical data of 276 patients with laboratory-confirmed COVID-19 infection were collected from El Obour Ain Shams University Specialized Hospital for Isolation records on admission from April 10, 2020 till July 30, 2020.

## Results

Fever was the most common presenting symptom (total number 135; 41.7%), followed by cough (total number 133; 41.2%). High CRP levels were predictive of higher COVID-19 severity and ICU admission ( $p=0.000$ ). Likewise, CRP levels were higher in patients with more chest affection as denoted by the CT chest findings ( $p=0.000$ ).

## Conclusion

Serum CRP is a simple and effective prognosticator which casts light on potentially critical patients. Consequently, it can be used to reduce the mortality of patients.

**Keywords:** COVID-19, Hospital, CRP, ICU, severity.

## What is already known about this topic?

C-reactive protein (CRP) is an acute inflammatory protein, which synthesized by the liver under the control of IL-6. It increases during infection or inflammation. Several studies show that CRP is not only a marker of infection and inflammation, but that CRP also has a protective role against bacterial infections. CRP usually increases in patients with COVID-19. It is one of the laboratory markers for diagnosis of COVID-19.

## What does this article add?

The current study reveals that CRP level is an effective prognosticator which can predict the severity of COVID-19 as denoted by the need for ICU admissions. For a theoretical conclusion to be reliable, it must be tested in different environments. The conclusion that the CRP level is of a prognostic value in COVID-19 has been reached via a reasonable number in the West. Nevertheless, it was neither examined in Africa nor in the Middle East. The present study is the first of its kind in this region. And, having reached to similar results to those studies conducted in other regions, our study adds more credibility needed for the conclusion to be reliable.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has escalated to acquire pandemic level since its first discovery in Wuhan, December 2019.<sup>1</sup> It has affected countless countries all over the world with rapidly increasing case fatality reports.<sup>2-4</sup> It is equipped with a vast spectrum of clinical manifestations, which varies from an asymptomatic presentation to a severe pneumonia along with multisystemic failure resulting into patient's death.<sup>5</sup> Nearly 20% of COVID-19 patients

possibly acquire life-threatening pathologies that involve acute inflammation, cytokine storm, septic shock complications, coagulation dysfunction, metabolic acidosis, hypoxia, and multiple organ failure.<sup>6</sup>

CRP is a pentameric acute-phase reactant protein produced by the liver, whose level increases as a response to IL-6 action on its gene transcription during an inflammatory/infectious process.<sup>7</sup> The rise in CRP level either alone or in conjunction with other inflammatory markers may denote bacterial or viral infections.<sup>9</sup> Multiple studies have assessed the prognostic value of CRP in both acute and chronic infections, hepatitis C, dengue, and malaria.<sup>10-12</sup> The elevation in its levels during infections conveys the extent of tissue involvement, thus, diagnosing bewildering complications.<sup>13</sup>

The inflammatory response plays a crucial role in COVID-19 progression. In addition, inflammatory cytokine storm increases the severity of COVID-19.<sup>9</sup> Hence, the identification of a simple and effective prognosticator is crucial for high lightening and treating the potentially critical patients, with the aim of reducing the mortality rate.<sup>13</sup>

The present study aims at investigating the capability of CRP to predict COVID-19 disease severity.

## METHODOLOGY

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

Subjects and Setting:

This is a retrospective cohort study where the clinical data of patients with laboratory-confirmed COVID-19 infection were collected from El-Obour Ain Shams University Specialized Hospital for Isolation records on admission from April 10, 2020 till July 30, 2020. Comorbidities as DM or hypertension, ICU admission, and treatment lines taken were documented, and considered in the data analysis.

All included patients in our study were laboratory-confirmed COVID-19 infection using reverse transcription polymerase chain reaction (RT-PCR). The patients were divided into three groups based on their disease severity according to Ain Shams University Hospitals Consensus Statement on Management of Adult COVID-19 Patients

- Mild cases: asymptomatic with abnormal lab. findings (D-dimer < 1mg/L, absolute lymphopenia < 800 / $\mu$ L, ferritin < 500 ng/mL, liver functions within normal) or HRCT findings of COVID-19 pneumonia OR symptomatic with no HRCT findings of COVID-19 pneumonia
- Moderate cases: Symptomatic with clinical signs of non-severe pneumonia (e.g. fever, cough, dyspnea) and HRCT findings of COVID-19 pneumonia and/or abnormal labs.
- Severe cases: clinical signs of severe pneumonia (e.g. respiratory rate > 30 breaths/min.; severe respiratory distress; or SpO<sub>2</sub> < 93% on room air) and HRCT findings of COVID-19 pneumonia

From April 10, 2020 till July 30, 2020, 338 patients were admitted at El-Obour Ain Shams University Specialized Hospital for Isolation. Only 323 patients had COVID-19 RT-PCR positives. The data collected and analyzed in the current study included sociodemographic data, detailed medical and drug history, presence of co-morbid conditions, laboratory investigations. These investigations included complete blood picture with differential count, blood group, CRP levels, serum d-dimer levels, ferritin levels, liver function tests, and kidney function tests. The current study assessed the correlation between CRP level on admission with the severity of the COVID-19, the risk for ICU admission and the findings of Computerized tomography (CT) chest.

CRP was measured by a commercially available latex-enhanced immuno-turbidimetric assay using an automated analyzer (BIOLIs 24i Tokyo Boeki, Japan). The normal value was <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. CT 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.

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 scores 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 present 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. 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 statistical methods were verified, assuming a significance level of  $p < 0.05$ .

## RESULTS

The present study included 323 patients. The mean age of the participants (total number 321) was 46.6 (SD 16.3) years and ranged between 10 and 85 years. Of the 323 COVID-19 patients, 171 (52.9%) were males and 152 (47.1%) were females. Only 21 (6.5%) were smokers and 302 (93.5%) were never smokers. Most of the patients (total number 302; 93.5%) reported contact with a confirmed case or cases of COVID-19 before diagnosis and hospital admission.

Fever was the most common presenting symptom (total number 127; 39.3%), followed by cough (total number 124; 38.4%). **Table 1** summarizes the presenting symptoms of all the patients.

CRP levels were measured for 276 patients with mean level of 42.26 (SD 68.90) and ranging between 1 and 710.

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** 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 CRP of  $60.17 + 92.83$  were patients regarded as moderately severe cases. Besides, the mean CRP level of  $91.29 + 81.96$  was present in severe cases of COVID-19, where patients having a mean CRP of  $101.97 + 107.56$  displayed the need for ICU admission. On the other hand, mild cases of COVID-19 had a mean CRP equivalent to  $20.53$  (SD  $2.48$ ).

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 CRP equivalent to  $67.47 + 90.04$ . In addition, those having grade 3 severity score showed a mean CRP equivalent to  $89.40 + 68.32$ . However, patients having free CT scans (grade 0 severity) or just grade 1 severity score CT findings had a mean CRP of  $18.66 + 25.59$  and  $8.93$  (SD  $4.32$ ).

## 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.<sup>14,21</sup> Since, the evolution of the clinical condition of these patients is difficult to forecast, early identification of prognostic indicators is an essential foundation to regulate treatment plans and promptly identify the severity of patients' condition.<sup>23</sup>

The present study included 323 patients. The mean age of the participants (total number 321) was  $46.6$  (SD  $16.3$ ) years and ranged between 10 and 85 years. Of the 323 COVID-19 patients, 171 (52.9%) were males and 152 (47.1%) were females. Only 21 (6.5%) were smokers and 302 (93.5%) were never smokers. Most of the patients (total number 302; 93.5%) reported contact with a confirmed case or cases of COVID-19 before diagnosis and hospital admission. Fever was the most common presenting symptom (total number 127; 39.3%), followed by cough (total number 124; 38.4%).

These results are in alliance with **Li and collaborators'** results. They conducted a study to analyze the epidemiologic data of the first 425 confirmed COVID-19 patients in Wuhan. Their results revealed that the male sex was the predominant sex among cases and fever was the most common symptom followed by cough.<sup>17</sup> **Guan and collaborators** similarly found that fever (87.9%) and cough (67.7%) were the most frequent presentations in a study conducted on 1099 COVID-19 cases<sup>15</sup>. Moreover, **Zhao and collaborators** also reported that fever and cough were the most common presenting manifestations.<sup>16</sup>

Several published epidemiological studies supported the current results showing low prevalence of smoking among confirmed cases.<sup>15,18-20</sup>

A cytokine cascade is the chief factor in COVID-19 induced hyperinflammation together with multiorgan failure.<sup>21</sup> The levels of certain blood markers (IL-1b, IL-6, IL-12, TNF-a ferritin) in decrepit patients during cytokine storm are elevated.<sup>22</sup> IL-6 is a cytokine having multifunction which is accountable for induction of liver cells to enhance synthesis and production of CRP.<sup>24-26</sup> Since, the assessment of CRP level is a part of admission work up in isolation hospitals, we assessed the correlation between CRP levels on admission and the severity of the COVID-19 together with the risk of ICU admission.

This study revealed that high CRP levels were predictive of higher COVID-19 severity 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 neutrophil to lymphocyte ratio (NLR), CRP, and platelets can efficiently evaluate the severity of COVID-19.<sup>27</sup> **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.<sup>9</sup>

Correspondingly, this research drew our attention to the fact that the correlation between CRP and the extent of chest affection via CT.CRP levels was higher in patients with more chest affection as denoted by the CT chest findings.

**Chen and collaborators** performed an observational retrospective study on 76 cases infected by SARS-CoV-2.<sup>28</sup> 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 significantly rose by 11.47 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.

## CONCLUSION

Serum CRP is a simple and effective prognosticator which casts light on potentially critical patients. Consequently, it can be used to reduce the mortality rate. Serum CRP has a predictive value of COVID-19's severity. As serum CRP increases the need for ICU admission increases. Patients with severely affected lungs have high CRP levels.

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**Conflicts of interest:** none.

## Authors' contributions

MF, SF and MM designed the study. ST, SF, MM, AH and SR shared in sample collection. AO performed the analysis and grading of the CT images. MF did the statistical analysis. SF and MF wrote the draft. RS performed the critical review of the manuscript. All authors reviewed and approved the final version. All authors read and approved the final manuscript.

## Availability of data and materials

All the data needed to support the current findings could be found in a supporting sheet.

## Consent for publication

Not applicable.

## Ethical consideration

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

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**Table 1. Presenting symptoms of admitted COVID-19 patients at Ain Shams University Hospitals.**

Symptom	Number	Percentage
Asymptomatic	36	11.1
Fever	127	39.3
Sore throat	1	0.3
Cough	124	38.4
Cough and Dyspnea	18	5.6
Diarrhea	6	1.9
Melena	1	0.3
Diabetic ketoacidosis	1	0.3
Fever and cough	3	0.9

Symptom	Number	Percentage
Fever and diarrhea	5	1.5
Sore throat and bone aches	1	0.3
<b>Total</b>	<b>323</b>	<b>100</b>

**Table 2. Comparison between CRP levels, ICU admission and severity at hospital admission.**

Variable	CRP levels (Mean + SD)	P value
ICU admission Yes No	<b>101.97 + 107.56</b> <b>25.67 + 40.32</b>	<b>0.000</b>
Mild Severity Moderate Severe	<b>20.53 + 2.48</b> <b>60.17 + 92.83</b> <b>91.29 + 81.96</b>	<b>0.000</b>
CT Chest Grade 0 Grade 1 Grade 2 Grade 3	<b>18.66 + 25.59</b> <b>8.93 + 4.32</b> <b>67.47 + 90.04</b> <b>89.40 + 68.32</b>	<b>0.000</b>