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C-reactive protein as an early marker of severity and outcome in patients with SARS-CoV-2 infection

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ABSTRACT

Background: Infection with SARS-CoV-2 is a leading source of illness and death in the world. Millions of people contract SARS-CoV-2 every day as the incidence of infection rises. The mortality rate is mostly attributed to respiratory failure. Many studies have been carried out to identify biomarkers that can be used in the early detection of at-risk patients. CRP is a sensitive inflammatory biomarker; however, it can be measured by simple, inexpensive methods that are widely available in hospitals. Therefore, it was selected for this clinical trial.
Methods: This retrospective cohort analysis included 100 patients who were accepted to El-Obour Ain Shams University Specialized Hospital for Isolation between May and October 2020. Admission CRP was investigated, and data were analyzed in relation to severity and mortality.
Results: Regarding history, older patients or those who had been diagnosed with hypertension, diabetes mellitus, chronic hepatic diseases, or active cancer have been statistically more prone to mortality. Concerning the laboratory investigations, those who did not survive had significantly lower haemoglobin levels and a higher TLC count. In addition, serum ferritin and D-dimer levels were significantly higher in the non-survivors. As regards CRP, the non-survivor group had significantly higher levels, with a cutoff value of >129 mg/l to predict mortality. It has also been correlated with severity in terms of need for ICU admission and need for respiratory support, with a cutoff value of >55.3 mg/L.
Conclusion: CRP can be used as a prognostic biomarker in patients with SARS-CoV-2 infection as it is a simple and effective predictor.

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C-reactive protein; SARS-CoV-2; COVID-19; mortality; severity

1. Introduction

In terms of both the population affected and the geographical distribution of epidemic regions, it has significantly surpassed SARS and MERS. The ongoing SARS-CoV-2 pandemic has caused a massive risk world health [1].

COVID-19 is an emerging infectious viral disease characterized as highly transmissible and deadly with no definite treatment; the prevalence and incidence of COVID-19 are having a significant effect on world health due to the insufficient recognition of its pathogenesis. Additionally, there is no trustworthy or practical biomarker to assess the condition, so it is vital to search the biomarkers for a progression predictor of the disease [2].

Severe cases of COVID-19 are mostly managed in the ICU, while patients who are not severe are managed in the usual isolation hospital unit or at home. A tiny subset of COVID-19 patients who do not have a severe illness, however, does. As a result, it is critical to identify and manage this subset of patients early to decrease illness severity and enhance outcomes [3].

The CRP marker is thought to be a significant marker in the early COVID-19 infection phases to predict the disease's clinical and radiological severity [4].

Several trials have highlighted the application of CRP in COVID-19 [5], as a significant correlation between CRP levels and the non-severe COVID-19 patients aggravation has been observed. The researchers suggested CRP as a suitable marker for predicting the probability that non-severe COVID-19 patients will aggravate [6].

2. AIM of the work

This study aimed to evaluate the C-reactive protein as an early marker for severity and outcome prediction in mild SARS-CoV-2 infection patients.

3. Materials and methods

Following the approval of the local ethics committee, this retrospective cohort study included 100 patients with SARS-CoV-2 diagnoses who were accepted to El-Obour Ain Shams University Specialized Hospital for Isolation between May and October 2020. We included

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patients with a confirmed mild infection of SARS-CoV-2 and a positive viral nucleic acid test at the time of hospitalization, as described in a Chinese CDC report. Patients with incomplete data or confirmed SARS-CoV -2 but other than mild disease were excluded.

The following procedures were performed on patients: taking a complete medical history; laboratory investigations such as a complete blood picture, CRP level (on admission), kidney function tests, liver enzymes, ferritin level, and INR; and radiological investigations such as a CT chest. Additionally, the need for oxygen therapy, mechanical ventilation, and ICU admission was recorded.

3.1. Statistical analysis

Data were gathered, revised, coded, and entered into IBM SPSS version 23. When parametric, the quantitative data have been shown as mean, standard deviations, and ranges; when non-parametric, they have been shown as median with interquartile range (IQR). Qualitative variables were also displayed using numbers and percentages. The p-value has been deemed significant as follows: P-values > 0.05 indicate non-significance, P-values ≤ 0.05 indicate significance, and P-values < 0.01 indicate highly significant.

4. Results

The previous table shows significant relation between mortality and raised levels of TLC, ferritin, D-dimer, and CRP with a p-value of 0.009, 0.00, 0.00, and 0.00, respectively, among the studied patients as shown in Table 1.

The previous table displays the relation between CRP level and comorbid conditions. It was found that hypertension, DM, IHD, active cancer, and CVS had a significant relation with CRP level with a p-value of 0.00, 0.00, 0.00, 0.01, and 0.03, respectively, as shown in Table 2.

The previous table displays the significant relation between CRP level and the occurrence of deterioration that requires ICU admission, oxygen therapy, mechanical ventilation, and the presence of radiological severity or even death with a p-value of 0.00, 0.00, 0.00, 0.00, and 0.00, respectively, as shown in Table 3.

The previous ROC curve shows that the best cutoff point for CRP to detect cases admitted to ICU was found >55.3 mg/L with sensitivity of 100.00%, specificity of 93.75% and area under curve (AUC) of 98.7% showing a positive predictive value of 80% and a negative predictive value of 100% as shown in Figure 1.

The previous ROC curve shows that the best cutoff point for CRP to detect need of mechanical ventilation was found >55.3 mg/L with sensitivity of 100.00%, specificity of 86.21% and area under curve (AUC) of 97.6% showing a positive predictive value of 52% and a negative predictive value of 100% as shown in Figure 2.

The previous ROC curve shows that the best cutoff point for CRP to detect mortality found >129 mg/L with sensitivity of 90.91%, specificity of 97.75%, and area under curve (AUC) of 98.1% showing a positive predictive value of 83.3% and a negative predictive value of 98.9% as shown in Figure 3.

5. Discussion

We studied 100 patients with mild SARS CoV-2 infection with age ranged from 18 to 81 years and with mean age of 41.51 ± 15.98, 48 males and 52 females.

In our research, we compared the CRP level at admission to mortality and found that the CRP level was significantly higher in patients who did not survive (11 cases, median CRP = 158 mg/L), compared to those who did (89 cases, median CRP = 9 mg/L). The cutoff point for CRP concentration on admission for prediction of death was reported as >129 mg/L, with a sensitivity of 90% and a specificity of 97.7%. This was statistically significant with a p value <0.00.

This finding was consistent with Han and colleagues [1] discovery that CRP levels predicted mortality with a cutoff value of >85.3 mg/L. Also, Pitre and colleagues

Table 1. Relationship between inflammatory markers and mortality.

		Fate				
		Alive No. = 89	Dead No. = 11	Test value	P- value	Sig.
TLC × 10^9/L	Mean ± SD	6.72 ± 2.89	9.25 ± 3.39	−2.683•	0.009	HS
	Range	2.2–16.2	5.1–14.6			
Ferritin µg/L	Median (IQR)	116 (55–250)	563 (164–1200)	−3.065≠	0.000	HS
	Range	7–1200	137–1200			
D-dimer ng/mL FEU	Median (IQR)	371 (200–696)	2300 (1185–3512)	−4.137≠	0.000	HS
	Range	38–6554	295–10,000			
CRP mg/L	Median (IQR)	9 (6–21)	158 (150–162)	−5.196≠	0.000	HS
	Range	1–152	56.5–200			
	Negative	30 (33.7%)	0 (0.0%)	5.297*	0.021	S
	Positive	59 (66.3%)	11 (100.0%)			

P-values > 0.05: Non-significant; P-values < 0.05: Significant; P-values < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann–Whitney test
FEU = fibrinogen equivalent unit (Positive CRP >6 mg/L)

Table 2. Relation between sex and comorbidities with CRP level.

		CRP				
		Median (IQR)	Range	Test value•	P-value	Sig.
Sex	Male	12.5 (6.5–68.5)	2–162	−1.047	0.295	NS
	Female	9 (5.75–51.15)	1–200			
HTN	No	9.5 (6–24.4)	1–180	−3.284	0.001	HS
	Yes	99.5 (8–151)	5.5–200			
DM	No	8.5 (6–20)	1–162	−4.366	0.000	HS
	Yes	110 (26–152)	6–200			
IHD	No	10 (6–38.5)	1–200	−2.710	0.007	HS
	Yes	104.5 (87–139)	12–162			
CKD	No	11 (6–47)	1–200	−0.870	0.384	NS
	Yes	110 (5.5–151)	5.5–151			
Asthma	No	11 (6–56.5)	1–200	−0.182	0.855	NS
	Yes	11 (6–18)	5–144			
CLD	No	11 (6–55.3)	1–200	−1.336	0.182	NS
	Yes	139 (139–139)	139–139			
COPD	No	11 (6–44)	1–200	−1.444	0.149	NS
	Yes	97.5 (46.5–135)	6–162			
Autoimmune	No	11 (6–56.5)	2–200	−0.203	0.839	NS
	Yes	10 (7.5–47)	1–158			
Smoker	No	11 (6–55.3)	1–200	−0.686	0.493	NS
	Yes	12 (7–59)	6–162			
HF	No	11 (6–41)	1–200	−1.932	0.053	NS
	Yes	87 (78–139)	78–139			
Active cancer	No	10.5 (6–44)	1–200	−2.475	0.013	S
	Yes	151 (85–152)	20–152			
CV stroke	No	10.5 (6–44)	1–200	−2.114	0.035	S
	Yes	82.5 (52–122.5)	26–158			

P-values > 0.05: Non-significant; P-values < 0.05: Significant; P-values < 0.01: Highly significant
•: Mann–Whitney test

Table 3. Relation between CRP level and complications.

		CRP				
		Median (IQR)	Range	Test value	P-value	Sig.
ICU admission	No	8 (6–18)	1–129	−6.722•	0.000	HS
	Yes	147 (109.5–158.5)	56.5–200			
O_2 need	No	8 (6–15.5)	1–129	−7.164•	0.000	HS
	Yes	139 (108–158)	56.5–200			
MV	No	9 (6–20)	1–152	−5.522•	0.000	HS
	Yes	152 (144–162)	56.5–200			
Radiological affection in CT chest (% of lung involvement)	Normal	8 (5.5–15.5)	1–129	39.031≠	0.000	HS
	<25	24.4 (6–89)	3–152			
	25–50	66.65 (11–109.5)	7.5–200			
	50–75	151.5 (132–160.5)	56.5–180			
	ARDS (>75)	154 (144.5–160)	139–162			
Outcome	Dead	158 (150–162)	56.5–200	−5.196•	0.000	HS
	Alive	9 (6–21)	1–152			

P-values > 0.05: Non-significant; P-values < 0.05: Significant; P-values < 0.01: Highly significant
•: Mann–Whitney test; ≠: Kruskal–Wallis test

[7] found that COVID-19 mortality was related to a CRP level of >78.4 mg/L but in a majority of severe COVID-19 cases. Markowicz and colleagues [8] found that mortality was associated with a CRP level greater than 100 mg/L with an unselected severity degree.

The diversity of CRP level that was associated with COVID-19 mortality across studies can be explained by different degrees of severity, stages of inflammation, presentation time, and presence of secondary bacterial infection or different covid-19 strains [9].

Our study reported a positive correlation between the admission levels of CRP and the need for different levels of respiratory support as well as oxygen therapy. The CRP level was significantly higher in those who needed respiratory support (23 out of 100) with a median CRP level of 139 mg/L than in those who did not need respiratory support, and the cutoff point for the CRP level on admission for predicting the need for respiratory support was reported to be >55.3 mg/L with a sensitivity of 100% and specificity of 86%, as well as being statistically significant with a p value <0.00. These results matched Liu and colleagues' [10,11] study, which had a majority of mild cases with an average age of 65.5 years and showed that a CRP level >41.8 mg/L can predict the need for respiratory support. Also, Wang and colleagues' (2020) study, which had a majority sample of mild cases with a mean age of 54 years, declared that a CRP level of >27 mg/L predicted the need for respiratory support. However, some studies have suggested higher levels of CRP to predict need of respiratory support, but it was related to the average CRP level during the course of disease as Herold and colleges [12] study which found that CRP level of >97 mg/L during

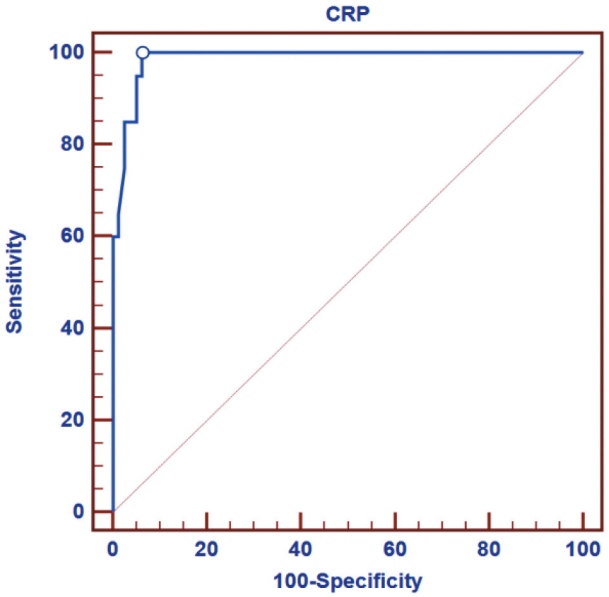

Figure 1. ROC curve for CRP to predict ICU admission.

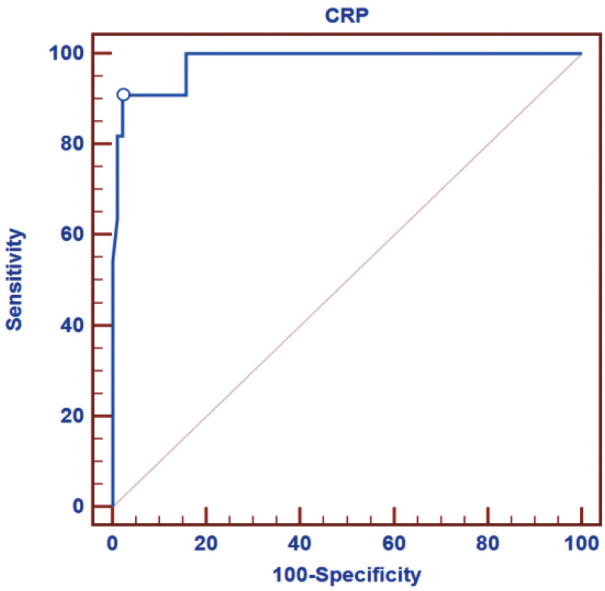

Figure 3. ROC curve for CRP to predict death.

hospitalization predicts need of respiratory support, in addition to Markowicz and colleges [8] study that found that respiratory support was needed in patients that had CRP level >100 mg/L; however, he had a smaller sample size.

The difference between the cutoff levels of CRP to predict the need for respiratory support is multifactorial, but it is mainly due to different withdrawal times of CRP as we studied CRP level on admission, but others studied mean CRP during hospital stay in addition to differences in the degree of severity, sample size, and age of the studied patients.

Moreover, we have correlated CRP level on admission with need for ICU admission, and it has been noted that the CRP level was significantly greater in patients who needed ICU admission (20 out of 100) with a median CRP level of 147 mg/L than those who did not need ICU admission, and the cutoff point for CRP level for predicting ICU admission was reported as >55.3 mg/L with sensitivity of 100% and specificity of 93%, and it was statistically significant with a p value < 0.000. This result has matched the study by Bahadirli and Kurt [13] which predicted ICU admission with a CRP level of >45 mg/L in a majority of individuals with mild illness with a median age of 76, and the Bayram and colleagues [14] study, which found that a CRP level of 113 mg/L predicts the need for ICU admission. In addition, Fouad and colleagues' [15] study has shown that a mean (±SD) CRP of 101.97 ± 107.56 mg/L predicts ICU admission needs.

Discrepancies in the cutoff values of ICU admission are likely to be due to differences in the threshold for ICU admission along with different comorbidities such as chronic diseases and presence of secondary bacterial infection.

Accordingly, this study called our attention to the fact that individuals experiencing more lung affection, as shown by the CT chest results, had higher levels of CRP that were correlated with the degree of lung affection measured by CT-CRP levels. It found a connection between pulmonary affection on CT chest and serum CRP levels. CRP levels significantly increased by 16.4 mg/L $p < 0.00$ when comparing mild CT results. Additionally, the moderate and severe CT affections each saw a significant 40 mg/L and 90 mg/L increase in serum CRP. These findings are consistent with those of a 2021 study by Fouad and colleagues, which discovered a positive relationship between CRP and pulmonary affection, and Chen and colleagues [16] study, which demonstrated that the higher the CRP, the greater the lung affection.

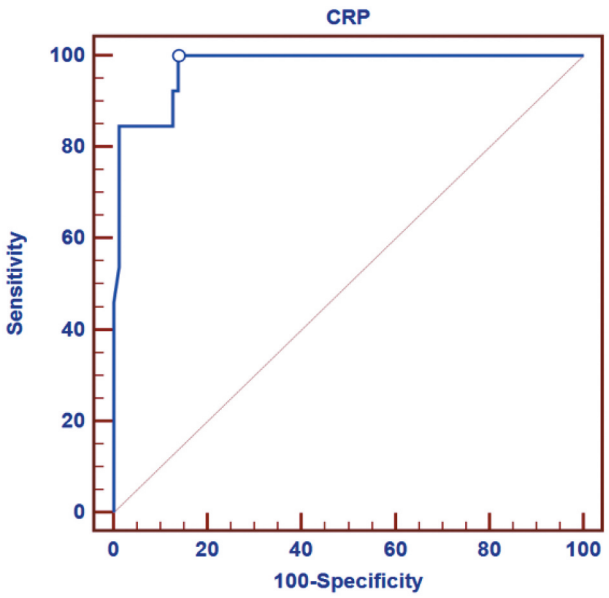

Figure 2. ROC curve for CRP to predict respiratory support need.

Finally, it is worth mentioning that we have to do more studies to explore the effects of the various new strains on the populations whether they were vaccinated or non-vaccinated with respect to differences in vaccines and the number of doses administered. In addition, we must overcome the limitations of previous studies such as small sample sizes, differences in time of recruitment to time of onset, selecting a specific degree of severity with respect to updates in management strategy and thresholds to different interventions such as ICU admission and respiratory-support.

6. Conclusion

We deduced from the current study that CRP on admission positively correlated with the need for ICU admission, the need for respiratory support, and the severity of CT pulmonary findings in SARS-CoV-2 infection cases. Additionally, CRP at admission was significantly higher in non-survivors, and it also had a prognostic role in SARS CoV-2 patients.

Thus, we can draw the conclusion that CRP is a simple and effective prognosticator that can be used to predict deterioration in mild cases of SARS CoV-2 infection.

Disclosure statement

The researchers state that they have no conflicting interests.

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