

LETTER TO THE EDITOR

Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19

To the Editor,

The outbreak of coronavirus disease-2019 (COVID-19) is an emerging global health threat. The healthcare workers are facing challenges in reducing the severity and mortality of COVID-19 across the world. Severe patients with COVID-19 are generally treated in the intensive care unit, while mild or non-severe patients treated in the usual isolation ward of the hospital. However, there is an emerging challenge that a small subset of mild or non-severe COVID-19 patients develops into a severe disease course. Therefore, it is important to early identify and give the treatment of this subset of patients to reduce the disease severity and improve the outcomes of COVID-19. Clinical studies demonstrated that altered levels of some blood markers might be

linked with the degree of severity and mortality of patients with COVID-19.¹⁻⁵ Of these clinical parameter, serum C-reactive protein (CRP) has been found as an important marker that changes significantly in severe patients with COVID-19.³ CRP is a type of protein produced by the liver that serves as an early marker of infection and inflammation.⁶ In blood, the normal concentration of CRP is less than 10 mg/L; however, it rises rapidly within 6 to 8 hours and gives the highest peak in 48 hours from the disease onset.⁷ Its half-life is about 19 hours⁸ and its concentration decreases when the inflammatory stages end and the patient is healing. CRP preferably binds to phosphocholine expressed highly on the surface of damaged cells.⁹ This binding makes active the classical complement pathway of the immune

TABLE 1 Levels of C-reactive protein (CRP) in patients with COVID-19

Reference	Group	Patients (n)	CRP, mg/L	P value	N and % of patients with elevated CRP
Chen et al ¹⁰	Hospitalized	99	51.4 (41.8)	NA	63/73 (86)
Chen et al ¹¹	Death	113	113 (69.1-168.4)	NA	59/68 (60)
	Recovered	161	26.2 (8.7-55.4)		21/45 (14)
Gao et al ¹²	Severe	15	39.4 (27.7)	.011	NA
	Mild	28	18.8 (22.2)		
Guan et al ¹³	Severe	173	NA	NA	110/135 (81.5)
	Non-severe	926	NA		371/658 (56.4)
Jin et al ¹⁴	Severe (GI symptoms)	74	15.7 (4.8-23.9)	.003	NA
	Non-severe (no-GI symptoms)	577	7.9 (2.6-19.6)		
Liu et al ¹⁵	Severe	13	62.9 (42.4-86.6)	NA	NA
	Mild	27	7.6 (3.1-57.3)		
Luo et al ¹⁶	Died	84	100 (60.7-179.4)	.000	NA
	Recovered	214	9.6 (5-37.9)		
Mo et al ¹⁷	Severe	85	46 (22-106)	.001	NA
	Mild	70	23 (10-47)		
Shang et al ¹⁸	Severe	139	43.1 (9.8-97.3)	<.001	NA
	Non-severe	304	10 (2.9-27.1)		
Shi et al ¹⁹	Hospitalized	81	47.6 (41.8)	NA	NA
Wang et al ³	Severe	16	43.8 (12.3-101.9)	.000	NA
	Non-severe	193	12.1 (0.1-91.4)		
Young et al ²⁰	Severe	6	65.6 (47.5-97.5)	NA	NA
	Non-severe	18	11.1 (0.9-19.1)		

Note: Data are presented as mean (SD) or median (IQR). Severe: patients admitted to the ICU. P value indicates the mean or median difference of CRP levels between the severe and non-severe group.

Abbreviations: GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range; NA, not available.

system and modulates the phagocytic activity to clear microbes and damaged cells from the organism.⁷ When the inflammation or tissue damage is resolved, CRP concentration falls, making it a useful marker for monitoring disease severity.⁷

The available studies that have determined serum concentration of CRP in patients with COVID-19 are presented in Table 1. A significant increase of CRP was found with levels on average 20 to 50 mg/L in patients with COVID-19.^{10,12,21} Elevated levels of CRP were observed up to 86% in severe COVID-19 patients.^{10,11,13} Patients with severe disease courses had a far elevated level of CRP than mild or non-severe patients. For example, a study reported that patients with more severe symptoms had on average CRP concentration of 39.4 mg/L and patients with mild symptoms CRP concentration of 18.8 mg/L.¹² CRP was found at increased levels in the severe group at the initial stage than those in the mild group.¹ In another study, the mean concentration of CRP was significantly higher in severe patients (46 mg/L) than non-severe patients (23 mg/L).²¹ The patients who died from COVID-19 had about 10 fold higher levels of CRP than the recovered patients (median 100 vs 9.6 mg/L).¹⁶ A recent study showed that about 7.7% of non-severe COVID-19 patients were progressed to severe disease courses after hospitalization,³ and compared to non-severe cases, the aggravated patients had significantly higher concentrations of CRP (median 43.8 vs 12.1 mg/L). A significant association was observed between CRP concentrations and the aggravation of non-severe patients with COVID-19 [1], and the authors proposed CRP as a suitable marker for anticipating the aggravation probability of non-severe COVID-19 patients, with an optimal threshold value of 26.9 mg/L.³ The authors also noted that the risk of developing severe events is increased by 5% for every one-unit increase in CRP concentration in patients with COVID-19.

Furthermore, it was observed that patients with low oxygen saturation ($SpO_2 \leq 90\%$) had significantly higher levels of CRP (median 76.5 mg/L) compared with patients with high oxygen saturation ($SpO_2 > 90\%$) (median 12.7 mg/L),²² indicating that more severe patients with lung damage have elevated levels of CRP. So, higher levels of CRP indicate more severe disease course-linked to lung injury and worse prognosis. CRP levels are correlated well with the severity of symptoms of patients with COVID-19; therefore, it may be a suitable marker in assessing a patient's conditions together with other clinical findings.


The elevated levels of CRP might be linked to the overproduction of inflammatory cytokines in severe patients with COVID-19. Cytokines fight against the microbes but when the immune system becomes hyperactive, it can damage lung tissue. Thus, CRP production is induced by inflammatory cytokines and by tissue destruction in patients with COVID-19. In conclusion, elevated level of CRP may be a valuable early marker in predicting the possibility of disease progression in non-severe patients with COVID-19, which can help health workers to identify those patients an early stage for early treatment. Besides, COVID-19 patients with elevated levels of CRP need close monitoring and treatment even though they did not develop symptoms to meet the criteria for the severe disease course. However, CRP levels in patients with COVID-19 who may progress from non-severe to severe cases need to be further studied in large-scale multicenter studies.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTION

NA wrote and revised the manuscript.

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