Nurshad Ali ORCID iD: 0000-0003-1649-0887

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

Nurshad Ali

Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology, Sylhet 3114, Bangladesh

Corresponding author

Nurshad Ali, Ph.D.

Department of Biochemistry and Molecular Biology,

Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh;

Phone: +880-1723205092

E-mail: nur_rubd@yahoo.com, nali-bmb@sust.edu

ORCID: https://orcid.org/0000-0003-1649-0887

To the Editor,

The outbreak of 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 (ICU), 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

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jmv.26097.

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 COVID-19 patients [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 6-8 hours and gives the highest peak in 48 hours from the disease onset [7]. Its half-life is about 19 hours [8] 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 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 fall, making it a useful marker for monitoring disease severity [7].

The available studies that have determined serum concentration of CRP in COVID-19 patients are presented in Table 1. A significant increase of CRP was found with levels on average 20-50 mg/L in patients with COVID-19 [10–12], Elevated levels of CRP were observed up to 86% in severe COVID-19 patients [10,13,14]. 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) [11]. The patients who died from COVID-19 had about 10 fold higher levels of CRP than the recovered patients (median 100 mg/L vs 9.6 mg/L). [15]. 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 mg/L 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 (SpO2 ≤90%) had significantly higher levels of CRP (median 76.5 mg/L) compared to patients with high oxygen saturation (SpO2 >90%) (median 12.7 mg/L) [16], 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 COVID-19 patients. 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 COVID-19 patients. In conclusion, elevated level of CRP may be a valuable early marker in predicting the possibility of disease progression in non-severe COVID-19 patients, 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 COVID-19 patients who may progress from non-severe to severe cases need to be further studied in large scale multicenter studies.

Conflict of interest: The author has no conflict of interest to declare.

Funding source: None

Author contributions: NA wrote and revised the manuscript.

Author ORCID: https://orcid.org/0000-0003-1649-0887

References

1. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. Published online April 25, 2020:jmv.25871. doi:10.1002/jmv.25871

2. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. *J Med Virol*. Published online May 22, 2020. doi:10.1002/jmv.26050

3. Wang G, Wu C, Zhang Q, et al. C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation. *Open Forum Infectious Diseases*. 2020;7(5):ofaa153. doi:10.1093/ofid/ofaa153

4. Ali N. Is SARS-CoV-2 associated with liver dysfunction in COVID-19 patients? *Clinics and Research in Hepatology and Gastroenterology*. Published online May 2020:S2210740120301406. doi:10.1016/j.clinre.2020.05.002

5. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *J Med Virol*. Published online April 8, 2020. doi:10.1002/jmv.25819

6. Marnell L, Mold C, Du Clos TW. C-reactive protein: Ligands, receptors and role in inflammation. *Clinical Immunology*. 2005;117(2):104-111. doi:10.1016/j.clim.2005.08.004

7. Young B, Gleeson M, Cripps AW. C-reactive protein: A critical review. *Pathology*. 1991;23(2):118-124. doi:10.3109/00313029109060809

8. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805-1812. doi:10.1172/JCI200318921

9. Ballou SP, Kushner I. C-reactive protein and the acute phase response. *Adv Intern Med*. 1992;37:313-336.

10. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7

11. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clinical Infectious Diseases*. Published online March 16, 2020:ciaa270. doi:10.1093/cid/ciaa270

12. Gao Y, Li T, Han M, et al. Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19. *J Med Virol*. Published online March 17, 2020:jmv.25770. doi:10.1002/jmv.25770

13. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. Published online March 26, 2020:m1091. doi:10.1136/bmj.m1091

14. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032

15. Luo X, Zhou W, Yan X, et al. *Prognostic Value of C-Reactive Protein in Patients with COVID-19*. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.03.21.20040360

16. Xie J, Covassin N, Fan Z, et al. Association Between Hypoxemia and Mortality in Patients With COVID-19. *Mayo Clinic Proceedings*. Published online April 2020:S0025619620303670. doi:10.1016/j.mayocp.2020.04.006

17. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7

18. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032

19. Jin X, Lian J-S, Hu J-H, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020;69(6):1002-1009. doi:10.1136/gutjnl-2020-320926

20. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*. Published online April 18, 2020. doi:10.1016/j.ebiom.2020.102763

21. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis*. Published online March 16, 2020. doi:10.1093/cid/ciaa270

22. Shang W, Dong J, Ren Y, et al. The value of clinical parameters in predicting the severity of COVID-19. *J Med Virol*. Published online May 21, 2020:jmv.26031. doi:10.1002/jmv.26031

23. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *The Lancet Infectious Diseases*. 2020;20(4):425-434. doi:10.1016/S1473-3099(20)30086-4

24. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA*. 2020;323(15):1488. doi:10.1001/jama.2020.3204

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. 2020 [17]	Hospitalized	99	51.4 (41.8)	NA	63/73 (86)
Chen et al. 2020 [13]	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. 2020 [12]	Severe	15	39.4 (27.7)	0.011	NA
	Mild	28	18.8 (22.2)		
Guan et al. 2020 [18]	Severe	173	NA	NA	110/135 (81.5)
	Non-severe	926	NA		371/658 (56.4)
Jin et al. 2020 [19]	Severe (GI symptoms)	74	15.7 (4.8-23.9)	0.003	NA
	Non-severe (no- GI symptoms)	577	7.9 (2.6-19.6)		
Liu et al. 2020 [20]	Severe	13	62.9 (42.4-86.6)	NA	NA
	Mild	27	7.6 (3.1-57.3)		
Luo et al. 2020 [15]	Died	84	100 (60.7-179.4)	0.000	NA
	Recovered	214	9.6 (5-37.9)		

Mo et al. 2020 [21]	Severe	85	46 (22-106)	0.001	NA
	Mild	70	23 (10-47)		
Shang et al. 2020 [22]	Severe	139	43.1 (9.8-97.3)	<0.001	NA
	Non-severe	304	10 (2.9-27.1)		
Shi et al. 2020 [23]	Hospitalized	81	47.6 (41.8)	NA	NA
Wang et al. 2020 [3]	Severe	16	43.8 (12.3-101.9)	0.000	NA
	Non-severe	193	12.1 (0.1-91.4)		
Young et al. 2020 [24]	Severe	6	65.6 (47.5-97.5)	NA	NA
	Non-severe	18	11.1 (0.9-19.1)		

Data are presented as mean (SD) or medians (IQR). Severe: patients admitted to the intensive care unit (ICU). GI: Gastrointestinal. NA: data was not available. P-value indicates the mean or median difference of CRP levels between the severe and non-severe group.