Review Article

A Review of CRP as a Biomarker of COVID-19

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Abstract

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 across the world. Patients with severe form of COVID-19 are generally treated in the intensive care unit, while mild or non-severe patients are treated in the isolation ward or at home. It is important to identify early and give treatment to reduce the disease severity and improve the outcomes. There is no credible and convenient biomarker to predict the severity of the disease. Therefore, the exploration of biomarkers is deemed necessary. We aimed to review the diagnostic and early prognostic value of C-reactive protein (CRP) in COVID-19 patients. In a number of studies, CRP showed different distribution feature and differences existed in various ages, clinical types and outcomes of COVID-19 patients. The present study reviews the role of CRP level as a marker in indicating the severity of patients with COVID-19.

Key words: *COVID-19; Biomarker; CRP; ICU.*

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Introduction

Coronavirus disease 2019 (COVID-19) has been declared a pandemic by World Health Organization. Coronavirus belongs to the subfamily of Ortho-coronavirinae in the family of Coronaviridae and the order Nidovirales. In 2003, a severe acute respiratory syndrome coronavirus (SARS-CoV) had caused the outbreak of severe acute respiratory syndrome.[1] In December 2019, an "unknown viral pneumonia" outbreak had been reported. Finally, a novel coronavirus was detected and the isolated virus was termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), characterized as highly contagious and deadly.[2] It comprises a large virus family causing infections of varying severity ranging from the simple common cold to more severe infectious diseases. Various subtypes of coronaviruses that can be easily transmitted from person to person have been identified in humans. Furthermore, many coronavirus subtypes are detected in animals, causing severe diseases in humans via animal to human transmission.[3,4] It is equipped with a vast spectrum of clinical manifestations, which varies from an asymptomatic presentation to severe pneumonia along with multi-systemic failure resulting into patient's death.[5] Nearly 20% of COVID-19 patients acquire life-threatening pathologies that involve acute inflammation, cytokine storm, septic shock complications, coagulation dysfunction, metabolic acidosis, hypoxia, and multiple organ failure.[6] A large group of these patients present with a sepsis syndrome and hypoxia, eventually requiring a higher level of care and invasive mechanical ventilation (IMV). So, to look for predictors that can guide us

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in allocating resources for these patients and be prepared in advance is crucial as the health system has been stretched to their limits. It has affected countless countries all over the world with rapidly increasing case fatality reports.[7] The early categorization of COVID-19 patients is mainly based on the identification of effective laboratory biomarkers which can efficiently predict disease severity and give the chance for timely treatment. It is of prime importance to define appropriate laboratory biomarkers capable of categorizing patients based on their risk.[8]

CRP: A Biomarker

Biomarkers are the biological parameters measured quantitatively in biological samples collected from patients. These are used in the management of many diseases as indicators that reflect the pathological course of the clinical conditions of patients. It is essential to determine the condition of patients on time by using hematological and biochemical biomarkers. Important biomarkers associated with COVID-19 disease are the hematological biomarkers like lymphocyte count, neutrophil count, neutrophil–lymphocyte ratio (NLR), inflammatory ones like C-reactive protein (CRP), immunological markers like interleukin (IL)-6 and biochemical markers D-dimer, troponin, creatine kinase (CK), as well as procalcitonin (PCT), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), and those particularly related to coagulation cascades in disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS). New laboratory biomarkers could be identified through the accurate analysis of multicentric case series; in particular, homocysteine and angiotensin II could play a significant role in this regard. Some studies have reported elevated WBC, CRP, lactate dehydrogenase (LDH), CK, and troponin to be associated with the severity of COVID-19. Among these laboratory parameters, serum C-reactive protein (CRP) has been found as an important marker that changes significantly in patients with severe COVID-19 disease.[9,10]

C-reactive protein (CRP), an acute phase glycoprotein produced by the liver in response to interleukin 6 (IL-6), is a useful marker of inflammation. It is commonly evaluated in clinical practice as a sign of serious bacterial infection, trauma and various chronic diseases in older adults. 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. Its half-life is about 19 hours and its concentration decreases when the inflammatory stages end.[11]

Among the patients who are infected by SARS-CoV-2, some did not show hypoxemia or respiratory stress during the course of COVID-19, indicating it being a multifaceted disease. Therefore, one reliable and convenient biomarker is needed to predict the severity of COVID-19 pneumonia. 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 identify early and give the treatment of this subset of patients to reduce the disease severity and improve the outcomes. 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.[12] Weiping et al.[13] suggested CRP levels as one of the first biomarkers to reflect physiological complications and as the most significant biomarker for predicting whether COVID-19 would progress.

Relation of CRP with COVID 19

Elevated levels of serum C-reactive protein (CRP) have been observed in patients with COVID-19 and used to assist with triage, diagnostics and prognostication. A significant increase of CRP has been found with levels on average 20 to 50 mg/L in patients with COVID-19. Elevated levels of CRP were observed up to 86% in severe COVID-19 patients. 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 whereas patients with mild symptoms had CRP concentration of 18.8 mg/L.[14,15] Stinger et al.[16] suggested a simple threshold of ≥40 mg/L should be used in clinical practice to guide disease severity and likely disease progression. Future studies should analyze using this simple threshold. This was a large multicentric study that included participants admitted to 13 hospitals. The demographics, case mix and mortality are similar to other larger studies reported within the UK, increasing the findings' generalizability. Using a threshold of ≥40 mg/L offered a high sensitivity and negative predictive value but low positive predictive value. A limitation of this study is that due to the urgent nature, disease severity on admission was only assessed using CRP without collection of circulating lymphocytes, interleukin-6, procalcitonin, serum lactate and viral load, all of which may also contribute to disease severity. In another study it was also observed that patients with low oxygen saturation (SpO2 ≤ 90%) had significantly higher levels of CRP (median 76.5 mg/L) compared with patients with high oxygen saturation (SpO2 > 90%; CRP median value 12.7 mg/L) indicating that more severe patients with lung damage have elevated levels of CRP.[17]

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.[18] 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. Liu et al.[19] also found a significant correlation between CRP and the severity of COVID-19 and suggested its use in predicting disease severity as an independent risk factor. Shang et al.[20] who studied the clinical records of 443 patients categorized into non-severe patients (n = 304) and severe patients (n = 139), had ascertained that neutrophil to lymphocyte ratio (NLR), CRP, and platelets can efficiently evaluate the severity of COVID-19.

Chen et al.[21] performed an observational retrospective study on 76 cases infected by SARS-CoV-2. 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 is significantly raised by 11.47 mg/L. Moreover, the serum CRP increased significantly by 23.40 mg/L in the moderate and severe CT affection. They concluded that the level of plasma CRP was positively correlated to the severity of COVID-19 pneumonia. It may be useful as an earlier indicator for severe illness and help physicians to stratify patients for intense care unit transfer.

Akdogan et al.[22] demonstrated that CRP levels were significantly higher in the severe group compared to the levels measured in the non-severe group, pointing out that the CRP level was an independent risk factor for the occurrence of severe COVID-19. Its levels positively correlated with acute lung injury in COVID-19 patients. It is a retrospective study conducted at a single-center and it reported that CRP levels were significantly high in most of the severe patients compared to non-severe patients. There were some limitations in this study. First, selection bias might occur for this retrospective study design, and further prospective studies were needed. Second, this study was based on a single center, and the number of patients participating in the study is not large enough, it should be supported by nationwide studies with a larger number of patients.

Ullah et al.[23] has done a retrospective cohort study to determine the association of CRP and D-Dimer with the need for invasive mechanical ventilation (IMV), dialysis, upgrade to an intensive care unit (ICU) and mortality. A total of 176 patients with confirmed COVID-19 diagnosis were included. They concluded that a high CRP value of >101 mg/dl at presentation appears to predict an increased need for IMV and intensive care. A high CRP value and elevated D-Dimer (>501 ng/ml) during hospitalization for COVID-19 predict higher odds of mortality; however, large scale and longer-term studies are needed to validate the findings.

Limitations

The findings of all the study should be interpreted in light of their limitations. Although the overall findings were adjusted for covariates, including baseline comorbidities and medications, the impact of unmeasured confounders could not be determined. Lastly, the interpretation might be limited by the sample size, age, sex, geographical difference, etc. 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.

Conclusion

An elevated level of CRP may be used as an important management tool as it can predict the possibility of disease progression in non-severe patients with COVID-19 at an early stage, which can help health workers to identify the patients at risk earlier and provide timely treatment. And this approach is likely to reduce the overall morbidity and mortality from severe COVID-19 disease. Besides, COVID-19 patients with elevated levels of CRP need close monitoring and treatment even though they do not develop symptoms to meet the criteria for the severe disease course.

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