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REVIEW ARTICLE

C-Reactive Protein a Promising Biomarker of COVID-19 Severity

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ABSTRACT

The 2019 coronavirus outbreak poses a threat to scientific, societal, financial, and health resources. The complex pathogenesis of severe acute respiratory syndrome coronavirus centers on the unpredictable clinical progression of the disease, which may evolve abruptly and result in critical and life-threatening clinical complications. Effective clinical laboratory biomarkers that can classify patients according to risk are essential for ensuring timely treatment, and an analysis of recently published studies found cytokine storm and coagulation disorders were leading factors of severe COVID-19 complications. The following inflammatory, biochemical, and hematology biomarkers markers have been identified in COVID-19 patients; neutrophil to lymphocyte ratio, c-reactive protein, procalcitonin, urea, liver enzymes, lactate dehydrogenase, serum amyloid A, cytokines, d-dimer, fibrinogen, ferritin, troponin, creatinine kinase, and lymphocyte, leukocyte, and platelet counts. These factors are predictors of disease severity and some are involved in the pathogenesis of COVID-19. CRP is an acute-phase, non-specific serological biomarker of inflammation and infection and is related to disease severities and outcomes. In the present study, CRP levels were found to rise dramatically among COVID-19 patients, and our findings suggest CRP could be utilized clinically to predict COVID-19 prognosis and severity even before disease progression and the manifestation of clinical symptoms.

INTRODUCTION

In December 2019, several pneumonia cases of unexplained etiology erupted in Wuhan city, China [1]. The causative pathogen now recognized as a novel coronavirus (nCoV), which was later renamed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus is now known as the major cause of coronavirus disease 2019 (COVID-19), a predominantly respiratory illness with adverse clinical outcomes [2].

Many COVID-19 patients do not exhibit signs or symptoms, or just mild symptoms. However, a subgroup of patients has suffered a severe illness, which often progressed into critical illness. Severe COVID-19 can be regarded as having a cytokine storm, multiorgan disease and disruption of numerous physiological pathways encompassing fibrinolysis and hemostasis [3-7].

Anomalies in several inflammatory, hematological and biochemical biomarkers have been observed in severe COVID-19 patients which can be utilized further for earlier identification of COVID-19 severity as well as to monitor adverse outcomes, mortality and prognosis of COVID-19 patients. The vital role of abnormal laboratory parameters in patients with COVID-19 has lately become apparent, and published studies recommend that particular clinical laboratory parameters may help in risk stratification and prog-

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nosis of these patients, ultimately leading to earlier interventions and the achievement of desired clinical outcomes [8-15].

Hence, early recognition and timely intervention of COVID-19 are crucial factors to prevent adverse clinical outcomes and burden on the scarce health resources due to the admission of a large number of patients in intensive care units. By incorporating these clinical laboratory biomarkers in routine testing, limited medical resources can be allocated to those COVID-19 patients who require urgent and timely treatment especially in the areas of epidemic origin.

In this short review, we focused more on C-reactive protein (CRP) and its correlation to COVID-19 severity as CRP levels found to be escalated in severe COVID-19 patients which is greatly associated with the severity of disease and disease progression.

MAIN ISSUE

1. Clinical distribution of COVID-19 patients

COVID-19 patients can range from mild to critical illness according to their clinical status.

1) Mild patients: general symptoms (fever, cough, nausea, loss of smell and taste), no respiratory symptoms, no abnormal chest findings.

2) Moderate patients: SpO2 >94% and an indication of abnormal chest x-ray and respiratory function.

3) Severe patients: SpO2 <94%, respiratory rate more than 30 breaths/min, PaO2/FiO2 <300 mm Hg, lung infiltrates more than 50%, require nasal cannula and high flow oxygen.

4) Critically ill patients: Acute distress respiratory syndrome, septic shock, cytokine storm, multiorgan failure intensive care unit is needed.

2. Laboratory biomarkers in severe COVID-19 patients

Abnormalities in several hematological, biochemical and inflammatory biomarkers have been observed in COVID-19 patients with serious illness compared with a mild disease, which provide clinicians with justification for inclusion of these biomarkers in risk stratification models. These biomarkers act as an important tool to detect patients who are on the verge of developing severe disease even before the manifestation of clinical symptoms in those epidemic areas which have limited health resources to carry out expensive laboratory and radiological examinations on COVID-19 patients. The CRP, albumin, LDH (lactate dehydrogenase), neutrophil to lymphocytes ratio, lymphocytes count, procalcitonin, albumin, thrombocytes and ferritin can be used to determine the severity of COVID-19. Decline in lymphocyte, thrombocytes, albumin, and increase in CRP, NLR (neutrophil-lymphocyte ratio), procalcitonin, D-Dimer, ferritin has been reported in COVID-19 patients [10, 15-22].

3. C-reactive protein

C-reactive protein is a pentameric acute-phase protein and acute pneumococcal pneumonia. CRP shows raised expression during inflammatory diseases such as some cardiovascular diseases, rheumatoid arthritis and somehow involved in their pathogenesis. C-reactive protein is synthesized predominantly in hepatocytes but also by other cell types such as adipocytes, lymphocytes, endothelial cells, macrophages, and smooth muscle cells. CRP levels can rise up to 1000 folds in any bacterial infection and decline abruptly as soon as infection resolves.

Recently published studies have recommended that CRP is not just a biomarker of infection and inflammation but it is also an important mediator of inflammatory processes. CRP exists in two unique isoforms, native CRP (nCRP) and monomeric, or modified CRP (mCRP), and the nCRP isoform has the ability to break down irreversibly into five mCRP subunits at sites of infection, inflammation and tissue damage. CRP acts as both pro-inflammatory and anti-inflammatory molecules depending upon which isoform of CRP is being released and active during infection and inflammation. CRP exhibits anti-inflam-

matory effects by mediating the activation of the complement pathway, apoptosis, phagocytosis, and pro-inflammatory effects by nitric oxide (NO) release and cytokine production [23].

CRP plays a critical role in the recognition of self and foreign molecules. This interaction leads to an activation of the adaptive immune system in inflammatory or infectious diseases. CRP has an affinity towards phosphatidylcholine ligands present on damaged cell membranes; exposed and denatured chromatin and small nuclear ribonucleoproteins. CRP plays a significant role in the clearance of these molecules through interaction with the complement system and Fc receptors on phagocytic cells [24]. Therefore, it has been suggested that CRP acts as a scavenger which is significant in clearing damaged membranes, decayed nuclear material, and autoantigens. CRP acts as an opsonin and helps to eradicate pathogens by phagocytosis through opsonization and activation of the classical complement pathway by which it protects organisms from infections.

Many studies have suggested CRP has been used as a prognostic biomarker in acute and chronic infections, including malaria, dengue, and hepatitis C [25-27]. On the other hand, mild elevation of CRP may or may not be clinically significant, depending upon the clinical condition of the patient. Clinical correlations must be taken into account while interpreting the CRP test results.

4. CRP and COVID-19 severity

1) IL-6 is the main inducer of CRP in COVID-19

Elevated levels of cytokines have been observed in COVID-19 patients, suggesting a cytokine storm [6] and exacerbating immune response towards viral infection in COVID-19 patients which is the crucial factor involved in the severity of COVID-19. Among them, IL-6 is the most significant cytokine which directly correlates with CRP levels in COVID-19 patients. The higher the level of IL-6, the greater the CRP in blood; Therefore, CRP as an indirect biomarker of IL-6 is sufficient and reliable to detect the severity of COVID-19 instead of measuring all cytokines in the body [28-30].

Measurement of CRP alone is the most practical tool to monitor disease outcomes in COVID-19 patients as it is obtainable, easy to interpret, and cost-effective rather than evaluating all cytokines which are costly as well as a time-consuming process and cannot be carried out in regions that do not have big setup to carry out complex prognostic tests.

2) CRP can predict the disease severity and outcomes in COVID-19 patients

CRP levels in COVID-19 patients can effectively predict disease severity, adverse outcomes, prognosis, and mortality. High CRP levels in COVID-19 patients at hospital admission indicate CRP can be utilized as an independent biomarker for earlier detection of disease severity [15, 31] as severe patients are more likely to have high CRP levels as compared to non-severe patients which indicate disease severity as well as the disease advancement [32]. High CRP levels in COVID-19 patients are strongly associated with the prognosis of COVID-19 which must be employed within the clinical practice to guide COVID-19 disease severity [33, 34].

Data published in recent studies suggest severe COVID-19 patients had high CRP levels relative to non-severe COVID-19 patients [31, 35-38], and similarly non-survivors had high CRP levels relative to survivors [39, 40], which indicates CRP levels in COVID-19 patients act as the best discriminator to distinguish severe patients from non-severe patients as well as non-survivors from survivors. High CRP levels in COVID-19 patients are strongly associated with mortality [41, 42] and its increasing levels are a risk factor for COVID-19 patients which is strongly associated with admission to ICU and death (Table 1).

Even in the absence of clinical history or radiological findings, we can anticipate COVID-19 outcomes by just looking at the CRP levels. Earlier detection of high CRP levels is the most appropriate method to detect

Table 1. CRP levels in mg/dL patients in severe, non-severe, survivor and non-survivor COVID-19 patients

Severe	Non-severe
43.15[a]	10.05[a]
1.4[a]	0.39[a]
0.54[a]	0.35[a]
8.64[a]	0.34[a]
54.60[a]	12.30[a]
Non-survivors	**Survivors**
12.05[b]	2.3[b]
19.4[b]	7.68[b]

[a]CRP levels in severe and non-severe patients which indicates that severe patients have high CRP levels as compared to non-severe [31, 35-38].
[b]CRP levels in non-survivors patients is high as compared to survivors [39, 40, 51].
After analysis of this data we can say although levels of CRP in mg/dL in severe, and non-survivor patients are vary in every publish article but these value are high in every article relative to non-severe and survivors and till now final threshold value to predict severe and non-survivors patients has not been decided yet.

COVID-19 patients, especially asymptomatic COVID-19 patients who are more vulnerable to develop severe disease. CRP can be used not only to monitor the prognosis of COVID-19 but also to discern severe patients from non-severe patients for risk stratification and better allocation of health services in areas that have reserved medical resources.

3) Combination of CRP with other biomarkers of severity in COVID-19

One of the striking features of CRP is it can be used in combination with other prognostic biomarkers to predict disease severity and published studies have recounted the fact that the predictive capacity of CRP was increased when it was combined with NLR, leukocytosis, serum amyloid A and ferritin to predict the prognosis of COVID-19 and vice versa. As patients with high NLR, leukocytosis, serum amyloid A and ferritin are more likely to develop severe disease so synergistic effect of CRP with these biomarkers can be used to improve the predictive capacity of CRP [34, 36, 43, 44]. Therefore, a complete panel of clinical biomarkers that are capable of detecting COVID-19 severity must be included in routine biochemical testing for earlier detection and timelier intervention of COVID-19 patients.

4) Correlation of CRP with computed tomography findings in severe COVID-19 patients

Rapid elevation of CRP in COVID-19 patients indicates aggressive immune response towards viral infection which is associated with lungs, kidney, and heart deterioration. The higher the initial CRP levels, the greater will be the pulmonary destruction and chances of having ARDS (acute respiratory distress syndrome). Thus, aggravated CRP in COVID-19 patients reflects lung destruction that should be regulated to prevent serious illness [44, 45]. Since the increase in CRP is positively correlated with pulmonary lesions, it can therefore be used along with the radiological findings to monitor disease progression. CRP is positively associated with the computed tomography (CT) grading score; CT scores increase as CRP increases, which makes it the best serological marker to monitor disease progression in an epidemic area having a massive number of COVID-19 patients but insufficient medical reserves for radiographic examination [15, 46].

As the CRP is positively associated with exacerbating immune response to viral infection and lung damage which makes it an even more sensitive clinical indicator of disease severity rather than CT grading itself [45], given that changes in CRP levels occur before the onset of pulmonary damage that has marked the significance of measuring CRP levels over time to detect the outcome of the disease even before the worsening of clinical condition.

5) Dynamic trends in CRP is predictive of COVID-19 severity

Dynamic trends in CRP are the most appropriate method to monitor COVID-19 patients, as CRP levels continuously tend to rise in progressive patients who initially presented themselves as mild patients and later develop severe disease.

It has been demonstrated in a study that dynamic trends in CRP are the best predictor of disease severity rather than initial CRP levels in predicting respiratory decline during hospitalization in COVID-19 patients and the change in CRP retains superior predictive value to either initial CRP value or the ROX (respiratory rate oxygenation) indices [30], as with every 1 unit increase in CRP in COVID-19 patients there is an increase in likelihood to shift from mild to severe COVID-19 disease [47].

Hence, serial measurement of CRP must be taken into account while monitoring COVID-19 patients as it is a highly convenient method for clinicians compared to complicated scoring systems and has the robust prognostic ability to predict respiratory failure among initially mild patients.

6) CRP tend to be high in men as compared to women suffering from COVID-19

Many elements can modify baseline CRP levels including age, sex, smoking status, weight, lipid levels, and blood pressure [48], after adjusting the baseline CRP levels, it has been detected CRP levels tend to be high among men relative to women suffering from COVID-19 [49, 50].

Data in recently published studies related to COVID-19 has shown men are more inclined to develop the severe disease as compared to women. We can assume that it may be due to high CRP levels that men are more prone to develop severe forms as compared to women but what is the actual reason behind the high ratio of men in severe COVID-19 yet to be identified.

7) Increased CRP levels indicates need for mechanical ventilation in COVID-19 patients

High CRP levels due to increased IL-6 release strongly predicts the need for mechanical ventilation in COVID-19 patients [51, 52], which indicates the likelihood of using CRP to guide treatment in COVID-19 patients who might need mechanical ventilation in future due to hyperinflammatory syndrome. That's why, CRP must be regulated in COVID-19 patients to prevent adverse outcomes.

8) Limitations

In this short review article, we have not mentioned single cut-off value of CRP needed to predict COVID-19 severity and prognosis as it has not been decided by health organizations yet. Similarly, as research is still undergoing on biomarkers of COVID-19 severity till now not a single biomarker with high prognostic value has been selected and approved to detect COVID-19 severity.

CONCLUSION

C-reactive protein is a convenient, economical, and easy to obtain prognostic biomarker that links with the disease severity and mortality. This can be used as an aid in clinical practice to guide treatment and monitor the COVID-19 patients in adjunct with other clinical parameters of prognosis and diagnosis. By doing so, we can improve prognosis and underrate mortality rates. We can conclude from the analysis of recent studies that a complete laboratory score consists of hematological, inflammatory and biochemical parameters must be taken into account to predict the severity and prognosis of COVID-19 patients irrespective of their clinical status for risk stratification and optimal allocation of health resource especially in the areas of limited health resources to improve clinical management and prevention of serious complications.

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