C-reactive protein in patients with COVID-19: A scoping review

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Abstract---The coronavirus illness 2019 (COVID-19) has spread to over 200 countries and infected over 70 million individuals since December 2019. The precise nature of the SARS-CoV-2 infection is yet unknown. In this study, we look at whether a C-reactive protein biomarker can predict clinical outcome or is linked to the severity of COVID-19 illness. Potential research published from the COVID-19 pandemic to May 2022 was found using the databases MEDLINE, Hinari, Google Scholar, and Google search. To extract relevant facts from each original report, a format established in a Microsoft Excel spreadsheet was employed. The retrieved data were transferred to STATA/MP version 16.0 software for further analysis. Keywords such as "COVID-19," "SARS-CoV-2," and "C-reactive protein," among others, were searched to find relevant papers. Only studies that reported mean C-reactive protein levels and COVID-19 disease stage results were included. The review contained twenty papers. All investigations indicated that individuals with severe COVID-19 had considerably greater levels of C-reactive protein than patients with

moderate illness. This review indicated that a specific biomarker may still be used to predict the risk of disease progression in asymptomatic and/or slightly too seriously unwell persons. The amount of C-reactive protein can be used to predict the chance of disease progression. The findings of this research indicated that C-reactive protein levels are an accurate biomarker for predicting the severity of COVID-19 illness. Although COVID-19 research is still in its early phases, physicians may find that investigating C-reactive protein levels throughout the illness course is critical for early diagnosis of severe symptoms and thereby improving prognosis. More large-scale investigations, however, are required to corroborate these findings.

Keywords---C-reactive protein, CRP, COVID-19, SARS virus.

Introduction

Multiple respiratory tract infection incidents with unknown causes were confirmed in Wuhan, China in December 2019 [1]. The virus in question is now known as a new coronavirus (nCoV), also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This pathogen has already been identified as a major source of COVID-19 illness, a lung infection with severe outcomes [2]. Several COVID-19 patients have neither symptoms nor clinical signs, or only flu manifestations. However, a subset of individuals developed a serious sickness that frequently progressed to severe disease. Extreme COVID-19 is characterized by interleukin waves, organ dysfunction disease, and destruction of many metabolic processes, including coagulation factors and blood clotting, [3-4].

According to recent research, CRP is significantly connected to the intensity of many illnesses. It is defined as a serum protein produced by hepatic endothelial cells that can be increased by a number of mediating factors, such as interleukin-6. CRP has previously been linked to chronic inflammation such as heart disease and Type II metabolic illness, as well as becoming a prognostic marker of acute infection. Furthermore, early plasma CRP growth has been demonstrated to enhance the chance of developing plasma leakage. As a result, CRP levels might be used to anticipate extreme bronchitis caused by COVID-19 [6]. Even though there would seem to be plasma indicators linked to high levels of intensity and death in this regard, CRP thresholds were markedly elevated in seriously SARS-CoV-2 susceptible individuals. [7]. COVID-19 pathological, physiological, and diagnostic approaches are at the discovery stage. [8] Clinical aspects can be interpreted more clearly when examined with biological markers such as CRP. As a result, investigating the CRP level may be critical for early identification and adequate therapy of COVID-19-related problems. The purpose of this paper is to look into CRP from the perspective of COVID-19 pathophysiology and to determine how it varies with the intensity of the illness.

COVID-19 patient: Clinical distribution

According to the clinical status of people suffering from COVID-19, they might have mild to severe sickness.

1. General symptoms (cough, fever, absence of taste and smell, nausea), no breathing difficulties, and no unusual chest observations in mild individuals.
2. Moderate patients have a SpO2 of > 94% and a chest x-ray and breathing feature tests that are abnormal.
3. Patients with a SpO2 of 94%, a ventilator ratio exceeds 30 breaths per minute, a PaO2/FiO2 of 300 mm Hg, and respiratory infiltrates exceed 50% require a nasopharyngeal catheter and elevated breathable air.

Acute respiratory distress, sepsis, interleukin wave, and organ's dysfunction need critical care department.

Biomarkers of COVID-19 among individuals with severe disease

In COVID-19 patients with significant disease, alterations in multiple hematological, metabolic, and proinflammatory cytokine markers have been reported, providing doctors with the reason for including biological markers in classification patterns. These indicators are essential for detecting people who are on the verge of developing serious illness even before clinical symptoms appear, especially in epidemic regions with minimal healthcare programs to do costly research lab and radiographic investigations on COVID-19 individuals. The severity of COVID-19 may be determined by CRP, albumin, lactate dehydrogenase, procalcitonin, neutrophil to lymphocyte ratio, transferrin, and clotting factors. In COVID-19 individuals, there was a decline in neutrophils, albumin, and clotting factors, as well as elevations in CRP, neutrophil-lymphocyte ratio, procalcitonin, transferrin, and D-Dimer [9, 10-11].

C-reactive protein

C-reactive protein is associated with acute pneumococcal pneumonia. CRP levels are elevated in inflammatory disorders, including heart disease and rheumatoid arthritis, and it may play a role in their etiology. Hepatocytes produce C-reactive protein, although other cell types such as adipocytes, interstitial cells, leucocytes, phagocytosis, and smooth muscle cells also produce it. CRP levels can rise by 1000 times during a bacterial illness and then drop sharply after the infection is over.

According to recent research, CRP is a key mediator of inflammatory conditions as well as a predictor of inflammatory disease. CRP comes in two forms: native CRP (nCRP) and monomeric (mCRP). At locations of inflammatory processes, and tissue destruction, the nCRP isoform can permanently degrade into five mCRP subtypes. Depending on whether the CRP isoform is generated during systemic inflammation, it serves as a pro-inflammatory as well as an anti-inflammatory molecule. CRP has anti-inflammatory properties by modulating complement activation, apoptosis, and phagocytosis, as well as pro-inflammatory properties by modulating NO release and cytokine synthesis [12].

CRP is important for recognizing both itself and other compounds. In inflammatory or infectious disorders, this contact activates the adaptive immune system. The binding sites of phosphatidylcholine, which are found on broken

cellular membranes, subjected and dissociated nucleosomes, are all targets for CRP. Through interactions with the signaling pathway and Fc neurotransmitters on phagocytes, CRP aids in the clearance of these substances [13]. As a result, it's been proposed that CRP functions as a scavenger, cleaning injured cell walls, degraded materials, and autoantigens. CRP is a type of activator that aids in the phagocytosis of pathogens by opsonizing and activating the traditional cellular supplement system that defends microbes from illness.

CRP was already recommended as a predictive indicator for a variety of physical and mental illnesses, such as dengue fever, malaria, and viral infections [14-15]. Mild CRP rise, on the other hand, may or may not be significantly meaningful, based on the patient's status. When evaluating CRP test findings, clinical correlations must be considered.

Status of CRP and COVID-19 illness progression

One retrospective single-center investigation in China revealed the statistical relevance of CRP for COVID-19. Most individuals with acute stages had considerably greater CRP levels than patients with non-acute illnesses (100 vs 9.65 mg/L), according to the research. [16] Another retrospective cohort discovered that severe clinical symptoms on CT scan had a higher level of CRP than moderate and mild clinical manifestations [15] . Furthermore, research conducted in Vietnam found that all COVID-19 patients, regardless of illness stage, had a greater extent of CRP [17]. In another Chinese study, individuals who died of COVID-19 had a higher CRP level (85.3 mg/L) than those who were improved and discharged (53.5 mg/L) in another Chinese study [18].

In research conducted in the USA, CRP level was found to be a quick, easy, and cost-consuming technique for estimating the amount of tissue damage in COVID-19 individuals [14]. Furthermore, a Turkish study found that inflammatory markers including CRP, among others, were linked to illness intensity and might be utilized as a possible predisposing variable for COVID-19 advancement [19]

The Severity of CRP and COVID-19

1. *In COVID-19, the primary inducer of CRP is IL-6.*

Increased cytokine levels have been seen in COVID-19 patients, implying a cytokine storm [20] and aggravating the immunological response to viral infection in COVID-19 patients, which is a key determinant in COVID-19 severity. IL-6 is the most important cytokine that has a direct relationship with CRP levels in COVID-19 patients. Because CRP as an indirect biomarker of IL-6 is adequate and reliable to identify the severity of COVID-19 instead of detecting all cytokines in the body, it is used to determine the severity of COVID-19 [20-21].

CRP measurement alone is the most practical tool for monitoring disease outcomes in COVID-19 patients because it is readily available, simple to interpret, and cost-effective, as opposed to evaluating all cytokines, which is both costly and time-consuming and cannot be performed in areas without a large setup to conduct complex prognostic tests.

2. *In COVID-19 patients, CRP can estimate the intensity and prognosis of the illness.*

CRP levels in COVID-19 individuals can accurately determine disease intensity, negative consequences, survival rate, and death. Elevated CRP levels at hospitalization in COVID-19 patients imply that CRP is used as an impartial diagnostic marker for identifying disease severity sooner [10, 22], as serious individuals have higher CRP levels than non-serious individuals, indicating illness intensity and progression. [23]. Individuals suffering from COVID-19 have elevated levels of CRP, which is associated with a poor prognosis, and this data must be used in medical care to direct the intensity of COVID-19 illness [24, 25]. Evidence from a number of studies suggests that extreme COVID-19 individuals had greater CRP levels than non-extreme individuals with COVID-19 [26, 27-28], and non-rescuers had significantly greater levels of CRP than rescuers [29, 30], implying that levels of CRP in patients suffering from COVID-19 are the ideal differentiator between extreme and non-extreme patients. Elevated CRP levels in COVID-19 patients have been linked to death [31, 32], and rising CRP levels are a risk factor for ICU admission and death in COVID-19 patients (Table 1). We may predict COVID-19 outcomes even without a clinical history or radiological abnormalities by simply looking at CRP levels. The most effective way for detecting the early diagnosis of elevated CRP levels is to detect the severity of COVID-19 and CRP at the same time.

Table 1 shows CRP values in mg/dL in COVID-19 patients with severe, non-severe, survivor, and non-survivor disease.

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. Levels of CRP in extreme and non-extreme individuals, with extreme individuals having higher levels of CRP than non-extreme individuals [31, 35-38].
b. In non-rescuers, levels of CRP are higher than in survivors [26, 27, 33].

After analyzing this data, we can conclude that, while CRP levels in mg/dL in extreme and non-rescuer individuals differ in each published study, these values are consistently greater when compared to non-extreme and rescuers, and a final cut-off point for estimating extreme and non-rescuer individuals has yet to be determined. Individuals suffering from COVID-19, especially those who

are without symptoms are at a higher risk of developing a serious illness. CRP can be utilized to not only monitor COVID-19 prognosis, but also to distinguish extreme individuals from non-extreme for treatment planning in places with limited medical resources.

3. In COVID-19, combining CRP with additional severity biomarkers

Among the most notable features of CRP is its ability to anticipate the severity of the illness when combined with other prognostic indicators. According to research literature, CRP's inferential volume is expected to increase when merged with NLR, neutropenia, plasma amyloid A, and transferrin to estimate the prognosis of COVID-19 and vise-versa. Those individuals are more prone to suffering a serious illness. CRP's synergistic impact with these indicators can be exploited to boost CRP's predictive ability [25, 34, 35, 36, 45]. As a result, standard biochemical testing should include a comprehensive panel of examinations able to identify the intensity of COVID-19 for earlier diagnosis and management of COVID-19 patients.

4. CRP relationship with computed tomography research results in COVID-19 people with acute disease

A fast increase in the level of CRP among individuals with COVID-19 shows a strong immunological response to viral infection, which is related to deterioration of the lungs, kidneys, and heart. The higher the initial CRP levels, the greater the lung damage and the likelihood of ARDS (acute respiratory distress syndrome). Thus, elevated CRP in COVID-19 patients indicates lung deterioration, which should be controlled to avoid major sickness [36,37]. Because a rise in CRP is linked to pulmonary lesions, it can be utilized in conjunction with radiological data to track disease progression. CRP increases as CT scores increase, making it the ideal serological measure to track disease development in an epidemic area with a large number of COVID-19 patients but limited medical reserves for radiographic testing [10, 38].

Because changes in CRP occur prior to the onset of respiratory injury, clinical outcomes can often be identified even before the severity of health manifestations [37].

5. COVID-19 severity is predicted by dynamic changes in CRP.

The level of CRP continually increases in patients with severe illness who initially appeared as moderate individuals but subsequently acquire extreme illness, making active CRP the most suited technique for monitoring COVID-19 patients.

Research found that vibrant patterns in CRP are a stronger indicator of illness intensity than preliminary levels of CRP in COVID-19 individuals, and that the alteration in CRP levels retains outstanding prognostic validity to either the preliminary CRP value or the ROX (breathing rate oxygen saturation) index values [21], as 1 unit rise in the level of CRP among patients with COVID-19 may shift the illness from mild to moderate and from moderate to severe. [39]

As a result, serial CRP measurement should be considered while monitoring COVID-19 patients since it is a much more convenient tool for doctors than elaborate grading systems and has a strong predictive potential to predict respiratory failure in initially mild patients.

6. Men with COVID-19 likely to have higher CRP levels than women.

In a hospital in Wuhan, China, 88 individuals with COVID-19 were studied in an observational study. As previously stated, the goal of the research was to compare aspects of COVID-19 in the epidemic phage to earlier data on phage start, and it discovered latent correlations between major baseline or laboratory markers and illness severity. Then we discovered many indicators regarding the severity of COVID-19 to aid physicians in quickly recognizing extreme individuals and focusing on the predicted management for each.

The median age of the 88 patients matched that of earlier studies [40]. Despite the fact that our study included more women, the critically sick group was still primarily made up of elderly men, suggesting that elderly men were more readily developed than critically ill patients [41, 42]. Age was shown to be positively connected with certain indices, including CRP, IL-2R, IL-6, LDH, IL-8, IL-10, and TNF-, suggesting that the severe inflammatory response occurs more frequently in the elderly. Although the p-value was not excellent, the BMI decreased in the severely sick group, which might be due to limited sample capacity. More data was needed to determine whether having a low BMI makes the condition worse. [43, 46]

According to data from newly released research on COVID-19, men are more likely than women to have the severe condition. We can speculate that males are more likely than women to acquire severe forms of COVID-19 due to high CRP levels, but the true cause for the greater level of males in extreme COVID-19 remains unknown.

7. In COVID-19 patients, elevated CRP levels signal the necessity for mechanical ventilation.

Elevated CRP levels associated with elevated IL-6 release significantly predict the need for respiratory support [33, 44, 47], implying that CRP could be used to guide therapy in COVID-19 patients who may require mechanical ventilation in the future due to hyper-inflammatory disease [48, 49, 50],. To avoid negative results in COVID-19 patients, CRP must be controlled.

Conclusion

C-reactive protein (CRP) is a low-cost, easy-to-measure predictive biomarker that links illness severity to mortality. This can be utilized in clinical practice to guide therapy and monitor patients with COVID-19, in addition to other clinical reasons for diagnosis and prognosis. We can improve diagnosis and lower death rates by doing so. Based on the findings of recent studies, we can conclude that a comprehensive laboratory score comprised of hematological, inflammatory, and biochemical parameters should be used to predict the severity and prognosis of COVID-19 patients regardless of their clinical status in terms of risk classification and optimal health resource allocation, particularly in resource areas such as health limited, in order to improve clinical management and prevent serious complications.

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