

C-reactive Protein in Elderly and Pregnant COVID-19 Cases: A New Role for an Old Marker

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Abstract

The clinical characteristics and prognosis of high-risk groups, including elderly and pregnant women, may vary according to the overall susceptibility of novel coronavirus. For that, numerous researchers worldwide have concentrated their efforts on finding a trustworthy biomarker that can determine the severity, prognosis, and survival of those affected. C-reactive protein (CRP), an inflammatory biomarker that showed higher levels in coronavirus 2019 (COVID-19) cases, underlay inflammation degree and was used to gauge the severity of COVID-19. In this review, we discuss whether CRP might have other uses in COVID-19 cases besides predicting the severity and the clinical outcomes among vulnerable risk groups. Doctors must analyze CRP levels along with the period of illness to identify those liable for rapid progress and be able to categorize case severity to guide the clinical decision to improve prognosis.

Keywords: C-reactive protein, diagnostic, elderly, pregnant, prognostic, therapeutic

INTRODUCTION

More than 420 million cases and about 5.9 million fatalities have been reported since China reported the first instances of the coronavirus 2019 (COVID-19).^[1]

COVID-19 infection can vary from asymptomatic to severe type of respiratory distress. Regretfully, besides vaccination as the most effective preventive approach added to social isolation and wearing protective masks, there are just a few therapeutic therapies available.^[2]

Age was related to death in the initial report in hospitalized Chinese patients, comparable to prior results from severe acute respiratory distress (SARS) illness. Increased age was an independent risk factor for death among older patients, with odds risk about twice for ages between 65 and 79 years as opposed to 50–64 years.^[3,4]

Geriatrics are an important susceptible population to coronavirus. Geriatric sensitivity to severe COVID-19 is due to age, which reduces immunity in several ways. Aging promotes inflammatory response to pathogens and decreases the effectiveness of infection suppression. There was a clear positive link between older ages and higher death rates.

Furthermore, many geriatrics have chronic conditions such as diabetes and hypertension, making them more prone to severe COVID-19.^[4,5]

Finally, several COVID-19 therapeutic techniques are ineffective in elderly individuals.^[6]

Understanding the warning signs of alarming COVID-19 in the elderly is critical for an effective and timely treatment plan. As a result, many scientists worldwide have focused their efforts on developing a reliable biomarker that can be depended on in detecting the severity of this condition.^[7] C-reactive protein (CRP) is a protein released by the liver and the cornerstone of every inflammatory response and a crucial part of the innate immune process. CRPs are the body's initial pathogen line of defense. Although structurally different from the immunoglobulin (Ig) molecule, CRP has functional qualities with the Igs, such as the capacity to stimulate

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agglutination, complement fixation, inducing capsular swelling in bacteria, and phagocytosis.^[8]

Triggered by tissue damage or infection, CRP concentrations can rapidly rise to more than 1000–3000 times higher than normal. The standard value of CRP in the blood is >10 mg/L, but it rises swiftly within 6–8 h and peaks 48 h after the illness begins.^[7] After stages of inflammation are passed, the concentration of CRP is down, and finally, the patient will recover. The severity of many diseases is significantly related to CRP. CRP synthesis can be stimulated by a variety of inflammatory mediators, including interleukin-6. Acute infection, a chronic inflammatory condition, and Type II metabolic disease have all previously been connected to CRP.^[9] Since its discovery, CRP has been considered a checking instrument for inflammation severity and a diagnostic adjunct.^[9,10]

Moreover, when CRP is released in plasma early, this enhances the chance of plasma leakage. Consequently, the prediction of severe bronchitis was detected by CRP.^[11]

Biological markers such as CRP can be utilized to assess and interpret clinical characteristics more precisely. Hence, knowing the CRP level may be pivotal for the timely assessment and appropriate treatment of COVID-19 complications. CRP estimation reflects:

1. The existence and severity of the inflammatory process
2. Allow distinction of inflammatory from noninflammatory
3. Treatment requirement
4. Assess prognosis and anticipate future risk.^[12]

Furthermore, anti-inflammatory or immunosuppressive medicines have little effect on CRP levels unless they decrease the activity of the underlying illness.^[13]

For these reasons, it is critical to comprehend CRP and how its level fluctuates according to illness severity in distinct categories. CRP is a disease biomarker for diagnosis, prognosis, and risk assessment. In this review, we will emphasize the role of CRP in high-risk groups (elderly and pregnant) to see if the inflammatory marker remains at the top of forecasting disease severity and explore other new roles for this inflammatory biomarker during the COVID-19 pandemic.

A SEVERITY AND PROGNOSTIC BIOMARKER AMONG THE ELDERLY

Mehraeen *et al.* conducted a systemic review that discussed risk factors for having a fatal outcome following COVID-19. Increasing age was one, and being a male was another risk factor.

Higher CRP was associated with a 1.02 (0.96–1.08) odds ratio for fatal outcomes.^[12]

Brandao's study compared the levels of CRP among patients with cases of COVID-19 pneumonia; its levels were significantly higher among deceased cases ($P < 0.0001$);

moreover, the levels were higher ($P < 0.0001$) among those who were intubated and admitted to the intensive care units (ICUs) compared with those who did not.^[14]

Ali^[15] discussed that higher serum CRP was seen in up to two-thirds of severe COVID-19 patients. In addition, CRP was significantly greater in severely infected cases compared to nonsevere cases, with a CRP level of 39.4 mg/L in severe cases vs. 18.8 mg/L in mild cases.

CRP levels were higher in cases where the illness had progressed to a severe stage. As a result, with a cutoff value of 26.9 mg/L, it can be a valid prognostic marker upon hospital admission. Furthermore, cases that ended in mortality had ten times higher CRP levels than recovered patients (median: 100 vs. 9.6 mg/L). The authors stated that for every unit rise in CRP concentration, there is an increased probability of experiencing severe illness episodes by 5%.^[15]

Wang *et al.*'s study^[16] examined CRP's role among different age groups: young, middle aged, and elderly; its levels were significantly higher in severe cases and those admitted to hospitals across all age groups. Geriatrics showed even more elevated CRP, which was correlated in univariate and multivariate analysis to severe forms of the infection; in addition, CRP predicts severe illness in geriatrics with an accuracy of 0.85.

Wang *et al.*^[17] conducted a retrospective analysis that included deceased COVID-19 cases and compared their features to those of surviving severe and critically sick cases in the COVID-19 treatment facility. Enrolled cases had a median age of 71 years and showed no specific demographic aspects among dead patients compared to those surviving severe and critically sick cases. Interestingly, male-to-female fatality rates were comparable. However, various laboratory values, including CRP, revealed significant variations. COVID-19-deceased patients showed greater levels of CRP and D-dimer.

The exaggerated inflammatory response and cytokine overproduction escalate CRP levels among severely infected COVID-19 cases. CRP levels increase when lung tissue is damaged, and many organs fail to function due to the overactivity of cytokines.^[18]

To summarize, CRP can differentiate severe cases or cases with aggressive course following the primary infection. Furthermore, CRP can predict the case mortality and be lower among those who survived severe infection.

C-REACTIVE PROTEIN AS A FOLLOW-UP BIOMARKER

Many acknowledge the immunological aspects of COVID-19, which results in what is known as the long COVID-19 syndrome. The patients suffered from nonspecific symptoms such as shortness of breath, general weakness, memory impairment, and loss of cognitive function: some reported symptoms related to the digestive tract and other symptoms. The disease may last several weeks or months following the

acute infection and evolve over time. Its prevalence is based on sex, age being higher among women and the elderly.^[19] Das and Verma^[20] conducted a prospective study on elderly patients after their acute infection recovery. The study recruited 90 cases aged over 60 years and subgrouped them according to computerized tomography (CT) scanning finding into mild, moderate, and severe cases.

They assessed the patients by CT and CRP levels. Their result confirmed increased CRP values among severe cases, which was linked to a higher score of high-resolution CT, indicating the valuable role of CRP in monitoring patient recovery.

TREATING SEVERELY ILL COVID-19 CASES WITH C-REACTIVE PROTEIN Apheresis

Concerning the SARS-CoV-2 induced by COVID-19, the CRP plasma concentration was reported to be increased, analogous to bacterial infections. In addition, CRP levels associate with a poorer prognosis in COVID-19 and have been shown to be a valid marker for various detrimental events, such as the necessity for mechanical ventilation. As a result, therapeutic targeting CRP was proposed early in the epidemic.^[21]

CRP apheresis is an extracorporeal treatment that specifically reduces CRP plasma levels with minimal adverse effects.^[22] As a result, CRP may now be addressed therapeutically and selectively. Recently, it was suggested as a treatment for severe SARS-CoV-2-induced pneumonia.^[23] Following the publication of three case reports reporting individual healing attempts (CRP apheresis in COVID).^[24] The average age of those patients was 62 years, and they all suffered from medical comorbidities. They were categorized as having a progressive COVID-19 course with failing lungs (the signs of severe lung infiltration in all cases) and a CRP >100. Depending on their CRP levels, these individuals received repeated apheresis procedures.^[23]

Surprisingly, those patients improved with an 85% reduction of their serum CRP; one out of seven cases passed away the rest showed signs of improvement in the radiological assessment of the lung.

The authors recommended that CRP apheresis be used as soon as possible following the development of severe COVID-19, which we presume is during the first 72 h. With a CRP level, the cutoff was more than 100 mg/L. Out of seven patients, six were discharged well. Their result opened the way for therapeutic targeting of CRP in the early stages of severe COVID-19 with no side effects and a case fatality of 14%, which dramatically decreases for those high-risk groups.^[24]

C-REACTIVE PROTEIN IN PREGNANT WOMEN WITH COVID-19

Pregnant women endure several physiological changes, the most prominent of which are modifications in immunity and hormones that maintain the survival and growth of the baby.^[25]

Pregnant women have a twofold increase in the lung-angiotensin-converting enzyme-2 receptor, an essential step in viral entry and cell replication. COVID-19 promotes destruction, inflammation, and bleeding in lung pneumocytes via those receptors.^[26]

Consequently, pregnant women are more susceptible to serious illnesses; even women with nonsevere COVID-19 are at risk for severe pneumonia, mortality, admission to the ICU, and oxygen support when compared to nonpregnant women. In addition to other adverse pregnancy outcomes such as preterm labor, particularly among cases with medical comorbidities such as preeclampsia and diabetes.^[27] There have been reports of severe maternal morbidity and perinatal mortality due to COVID-19. According to evidence, pregnant women infected with COVID-19 may exhibit identical symptoms to the general population.^[28]

Infection severity and parity were substantially related to bad obstetric and newborn outcomes; older age pregnant women were more likely to suffer moderate-to-severe infection than those with asymptomatic or mild signs of the disease.^[29] The gestational age at which the infection occurred was also influential to the severity of the infection; case severity was highest among cases in the third trimester. However, the effect of parity was contradictory in some studies, and ethnicity was not influenced obstetric outcomes.^[30]

In line with earlier reports among the general population, higher CRP levels in seropositive mothers were significant parameters linked with the severity of the infection.^[31]

One of the laboratory predictors of maternal mortality is CRP; deceased mothers had increased CRP levels than those who survived, indicating more severe infection and inflammatory reactions. Furthermore, they may reflect an underlying cytokine storm in COVID-19, characterized by severe clinical features, including acute respiratory distress syndrome, multiple organ dysfunction syndromes, and maternal mortality.^[32-34]

Yamamoto *et al.* examined the prognostic value of higher CRP and low platelet counts in assessing the need for inpatient treatment alongside starting the medical intervention, including O₂ supply or the addition of systemic steroids or fluid supply owing to high-grade temperature or a sequel of the infection.^[30] At a criterion of 1.280 mg/dl, CRP predicted pregnant women that needed patient treatment with 81% sensitivity and 100% specificity and a reliable area under the curve of 0.9. The authors proposed a triage management treatment (weeks of gestation; blood test results: CRP levels and platelet counts) that will help risk categorization for seropositive cases during a crisis to handle many cases and prioritize admission for high-risk groups based on the model proposed.^[30]

Kim *et al.* examined the usefulness of CRP and ferritin levels among seropositive cases admitted to the hospital in a retrospective study design. The authors found that CRP and serum ferritin are linked with adverse pregnancy outcome (such as pneumonia and admission to ICU).

Moreover, they confirm they are reliable predictors of poor prognosis in COVID-19-seropositive mothers during the third trimester.^[35]

It is interesting that CRP and ferritin could predict poor outcomes even if the pregnant symptoms were mild or if the patient had an asymptomatic infection, which highlights its role in guiding the design plan of treatment.^[35-37]

CONCLUSION

CRP is a low-cost, easy-to-measure predictive biomarker that links COVID-19 severity, progression of infection, and predicted mortality upon hospital admission. It can guide the clinical decision to prescribe medication and follow COVID-19 patients. It was implemented during the rehabilitation of geriatric patients and was therapeutically targeted in severely ill patients; as for pregnancy, it had diagnostic, prognostic roles in addition to serving as a predictor of adverse pregnancy outcomes.

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Conflicts of interest

There are no conflicts of interest.

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