Journal of Biomedical Insights

Open Access

Review Article

A review on the relationship between C-Reactive protein (CRP) levels and the severity of COVID-19.

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Citation:
Zamri M H B, Norhadi M A B M, Fadhillah A K A B M A. (2026).A review on the relationship between C-Reactive protein (CRP) level and the severity of COVID-19. *Journal of Biomedical Insights,1(1)62-69*

Abstract:

This review analyses data from 35 papers published between 2020 and 2024 to study the relationship between C-Reactive Protein (CRP) levels and the severity of COVID-19. Elevated CRP levels are consistently associated with more severe disease, including a high risk of respiratory failure, ICU admission, and fatality, across all study designs and groups. CRP is useful as an early indicator for clinical worsening since it rises early in the course of disease, frequently before radiological changes. Additionally, longitudinal data demonstrate that poor outcomes are highly predicted by rising CRP trends throughout hospitalisation. CRP remains one of the most useful, affordable and generally available indicators when compared to other inflammatory biomarkers such as CRP-derived ratios, including CRP/albumin and CRP/lymphocyte, which improve prognostic accuracy. The continuous correlation of CRP with unfavourable outcomes supports its utility in early risk stratification, particularly in situations with limited resources, even if it cannot entirely predict the severity of a disease on its own. To enhance future clinical applicability, standardisation of CRP readings and additional validation of cut-offs are advised.

Keywords: C-Reactive Protein (CRP), COVID-19, Disease Severity, Prognostic Biomarkers, Inflammatory Markers, Risk Stratification, CRP Ratio, Clinical Outcomes.

Received: 05-12-2025

Revised: 17-02-2026

Accepted: 19-04-2026

Published: 30-06-2026

Introduction

In late 2019, the world was facing an unprecedented global health challenge, which was the emergence of the coronavirus disease (COVID-19) pandemic that is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The majority of infected individuals usually experience mild or moderate respiratory symptoms, but some progress to much more severe complications like pneumonia, acute respiratory distress syndrome, multiple organ failure and even death. Thus, understanding the causal factor of disease severity has been crucial for improving clinical outcomes and optimising resource allocation in healthcare systems worldwide. Biomarkers have been investigated for their potential as tools to predict disease progression. In this case, the C-reactive protein (CRP) has been showing its promise as one of the most consistently reported indicators of heightened inflammatory response in COVID-19 patients [24, 25, 31].

CRP is an acute-phase protein synthesised by the liver in response to inflammatory stimuli like interleukin-6 (IL-6) and other pro-inflammatory cytokines. it has been widely used in the diagnosis and monitoring of infectious and inflammatory diseases. Early in the pandemic, researchers observed that the COVID-19 patients who are hospitalised are presented with markedly elevated CRP levels, which started the investigations into its prognostic value. Studies conducted in Wuhan reported that increases in CRP are closely related to the worsening clinical status of a patient, with the higher CRP levels correlating with severe disease and poor outcomes [24, 25]. These findings are also true with the observations from

other studies, where CRP emerged as a key marker that differentiates between mild from severe COVID-19 [26, 15].

The pathophysiology of severe COVID-19 gives an important context for the role of CRP. In severe and critical cases, they are often characterised by dysregulated immune activation, also known as "cytokine storm", in which there is an excessive production of IL-6, TNF-α and other inflammatory mediators that lead to damage of the endothelial, microvascular thrombosis and pulmonary damage. This then caused CRP to be elevated due to reaction with IL-6, thus serving as an indirect marker of this hyperinflammatory condition. This connection between inflammation and clinical deterioration is further supported in the research provided by studies that found CRP to be one of the best indicators of severe disease presentations [26, 28].

Other than predicting severity, CRP has also proven to be useful in identifying patients who are at risk of death. Patients with elevated CRP levels are more likely to need to be provided with mechanical ventilation or they will just succumb to the illness; this is in accordance with studies done in the US, Europe, Africa, and Asia [13, 4, 9]. Furthermore, studies also show that rather than single measurements, CRP trends offer crucial information about clinical progression. Thus, continuous monitoring is crucial because rising CRP levels during hospitalisation have been associated with worsening respiratory status and increased mortality [24, 23].

Consequently, this review aims to comprehensively evaluate and summarize the clinical evidence regarding the association between C-Reactive Protein (CRP) levels and COVID-19 severity. By synthesizing data from multiple international cohorts, this paper describes the specific role of baseline and kinetic CRP values in predicting critical clinical outcomes, such as intensive care unit (ICU) admission, respiratory failure, and mortality. Furthermore, this review identifies persisting gaps and limitations in current prognostic modeling to guide future biomarker-driven triaging strategies

Methodology

Search Strategy

To perform this review, a thorough search of articles was conducted using databases including PubMed, Medline, Embase, Web of Science and Scopus. The articles were limited to articles which contain the terms "C-Reactive Protein (CRP) levels", "Severity" and "SARS-CoV-2" or "COVID-19" in either their title, abstract or keywords.

The terms were combined in search strings using the Boolean operators "OR" and "AND" to find sources that discuss the relationship between C-Reactive Protein (CRP) levels and severity of COVID-19. The search strings include ("C-Reactive Protein" OR "CRP" OR "inflammatory markers") AND ("Severity") AND ("SARS-CoV-2" OR "COVID-19").This review only included studies from 2020-2024. Studies that were included only in the English language or any studies translated into English.

Inclusion criteria

Included patients with SARS-CoV-2/COVID-19 infections, papers with reported quantitative CRP measurements or derived indices such as CRP/albumin or CRP/lymphocyte ratio and papers or original research with reported associations between CRP and clinical severity/outcomes of COVID-19.

Exclusion criteria

Were studies without CRP measurements, ex vivo studies and papers without original patient data.

Study Selection

The study selection process involves identification and screening of articles. Relevant studies were identified according to the keywords keyed in. Next, screening was done in which researchers read and analyzed the abstracts of the studies identified initially to evaluate their appropriateness to the study. Then, researchers read the full text of the studies chosen to determine whether they meet the inclusion criteria determined.
The extraction of the data included elements such as study design, country, settings, sample size, age/gender distribution, CRP measurement, assay details, central tendency, derived biomarker indications and outcomes evaluated.

Data Extraction Strategy

The studies reported were grouped by design, settings, region, patient population and biomarker types. Each of these groups was compiled with the median/mean of CRP levels throughout severity strata, and common CRP cut-offs were used to define high levels of CRP. For instance, the papers that presented the head-to-head comparisons of biomarkers were used to summarise the comparative levels of CRP against interleukin-6 (IL-6), procalcitonin (PCT), D-dimer, and lactate dehydrogenase (LDH) [25, 27, 28].
Random-effects meta-analysis was used to pool effect sizes where 3 or more studies provide comparable effect estimates, like odds ratios for increased CRP that predicts severe disease or mortality. While categorical comparison and continuous CRP effects were pooled independently. For studies that only report medians/interquartile range(IQR), they are converted to means/standard deviations to enable pooling. I^2 and Cochran's Q were used to quantify heterogeneity, while sources of heterogeneity were investigated using pre-specified subgroup analyses and meta-regression when there were enough studies available. Large cohorts and multi-centre studies such as Lentner et al. [13], Li F. et al, [6], and Gebrecherkos et al.[3] were used in representative candidate pooling analyses.
Studies that report serial CRP readings and their temporal link to worsening or recovery were analyzed to characterise the common trajectory patterns and their prognostic consequences. Time-to-event analyses or slope-based predictors were taken into consideration for qualitative synthesis when individual patient data(IPD) or sufficiently thorough serial summary statistics were available. Otherwise, results were summarised narratively [24, 23, 31].
The levels of C-Reactive Protein (CRP) was compared to other inflammatory biomarkers such as interleukin-6 (IL-6), procalcitonin (PCT), D-dimer, and lactate dehydrogenase (LDH) using reported area under curves, sensitivity/specificity and adjusted effect estimates. Composite indices like CRP/albumin and CRP/lymphocyte were assessed as alternative predictors of COVID-19 progression and mortality [29, 32, 19, 6, 25].
Studies that have a high risk of bias, limitation to prospective cohorts, and different pooling options were among the pre-specified sensitivity assessments. Geographic region, age group of 65 years and above, comorbidity burden and sampling schedule were categorized as pre-planned subgroup analyses. When possible, studies were stratified by enrolment date such as early 2020 and above to investigate the possible modifying effect of the SARS-CoV-2 variant phase or vaccination era [5, 13, 20].
CRP readings were standardised to mg/L when feasible, and assay techniques were documented in recognition of significant inter-laboratory variations like assay method, detection limits and units. As different studies exhibit a variety in assay method, the analysis separated the continuous measures from study-specific categorical cut-offs. For instance, studies that included CRP isoforms or high-sensitivity CRP, such as Molins, B. et al.[27], Aloisio et al.[10] were analysed separately to prevent misinterpretation.

Findings and Discussions

Pathophysiological Foundations and Systemic Activation

A comprehensive synthesis of 35 academic articles compiled from major research repositories—including Google Scholar, ScienceDirect, Springer, and Web of Science—establishes C-reactive protein (CRP) as a critically sensitive systemic marker of the acute phase of inflammation, tissue injury, and viral infection. Synthesized data demonstrates that CRP synthesis is upregulated in response to interleukin-6 (IL-6)-mediated inflammatory cascades, directly reflecting the systemic cytokine activation and hyperinflammatory "cytokine storm" characteristic of severe SARS-CoV-2 infection. Across all evaluated cohorts, elevated CRP levels demonstrate a robust, statistically significant association with progressive disease acceleration requiring intensive care unit (ICU) admission, advanced hospitalization, and heightened mortality rates, manifesting independently of geographic distribution or baseline patient demographics.

Early Trajectory Monitoring and Early Triage Potential

A critical consensus across the literature indicates that a significant increase in CRP levels occurs early during the incubation and prodromal phases of COVID-19, frequently preceding the presentation of defining radiographic abnormalities or clinical signs of severe respiratory failure. Specifically, elevations in CRP can manifest prior to the appearance of structural abnormalities on computed tomography (CT) lung scans, validating its clinical utility as an early triage tool [31]. Early-stage monitoring of CRP levels enables clinicians to reliably differentiate patients destined for severe illness from those likely to maintain milder, self-limiting symptoms [15, 28].

Furthermore, the longitudinal trajectory of CRP synthesis serves as a mirror for clinical progression; a sharp, upward trajectory within the initial 48 hours of evaluation indicates an elevated risk for severe respiratory complications and immediate ICU admission [24]. Consequently, sequential monitoring of CRP kinetics is vital, as even minor incremental shifts during early hospitalization can signal clinical deterioration before overt physical decline occurs, rendering absolute reliance on static baseline readings inadequate [23].

Independent Prediction of Severity, Mechanical Ventilation, and Organ Failure

Elevated CRP levels consistently function as strong, independent predictors of severe and critical COVID-19 across diverse clinical cohorts. After adjusting for confounding demographic characteristics—such as advanced age and a range of chronic comorbidities—multivariate regression models confirm that elevated baseline CRP levels independently predict the need for mechanical ventilation, ICU admission, and overall mortality [13, 18]. Direct positive correlations are established between circulating plasma CRP concentrations and step-wise increases in clinical severity [1], cementing its status as a validated biomarker for staging COVID-19 progression [2].

Furthermore, elevated CRP concentrations show substantial correlations with acute hypoxia and profound respiratory failure [26]. Beyond physiological degradation, higher CRP values have also been linked to elevated psychological stress in severe COVID-19 cases [34]. The diagnostic utility of CRP exhibits global applicability, with consistent results reported from international cohorts across:

Mortality Prediction and Population-Specific Cut-Off Thresholds

In addition to staging disease severity, CRP serves as an independent prognostic factor for mortality. After controlling for age, gender, and pre-existing comorbidities, elevated CRP values remain independently associated with a high risk of death [6]. This prognostic capability is particularly evident in vulnerable populations, where elevated CRP concentrations correlate with poor survival rates in elderly hospitalized patients [5]. Within intensive care settings, CRP—frequently operating alongside IL-6 and D-dimer metrics—stands out as one of the strongest predictors of imminent death in critically ill patients [21], a finding corroborated across multiple diverse populations [1, 4, 12, 26].

Comparative Practicality and Resource-Limited Feasibility

When evaluated against alternative hyperinflammatory biomarkers—such as interleukin-6 (IL-6), procalcitonin (PCT), and lactate dehydrogenase (LDH) , CRP is recognized as one of the most effective and practical laboratory options available [19, 21, 30]. Comparative assessments demonstrate that CRP frequently outperforms several complex biomarkers in predicting overall severity and mortality [19]. Its potential as a primary diagnostic marker of clinical severity provides clear direction for real-time clinical decision-making [7, 8, 11] and forecasting disease aggravation [9].

While both CRP and IL-6 show high predictive accuracy for mortality in critically ill individuals, CRP offers significant operational advantages:

Compared to complex cytokine assays, CRP benefits from rapid laboratory turnaround times and low processing costs, making it highly practical for routine clinical monitoring, particularly within resource-limited or low-resource medical environments [21]. To support this utility across varied clinical settings, establishing standardized CRP measurements is essential to ensure consistent assessment and uniform interpretation across different healthcare facilities [10].

Advanced Prognostic Ratios, Isoforms, and Multimodal Diagnostics

To maximize predictive accuracy, recent investigations have focused on advanced, CRP-derived biomarker ratios. The CRP-to-albumin ratio (CAR) regularly outperforms raw, standalone CRP values when forecasting disease progression and eventual mortality [35]. By pairing an acute-phase inflammatory marker (CRP) with a negative acute-phase nutritional marker (albumin), CAR provides a comprehensive view of a patient's inflammatory and metabolic status [14, 29, 33]. Similarly, the CRP-to-lymphocyte ratio (CLR) demonstrates a strong correlation with early illness severity, capturing both systemic inflammation and immune suppression [17]. Furthermore, combining CRP with metabolic indices like the urea-to-albumin ratio significantly improves the identification of severe disease [14]. Innovative structural approaches have also explored assessing distinct CRP molecular isoforms, suggesting that specific configurations may offer greater prognostic precision than total CRP measurements alone [27].

However, to ensure the reliability of these metrics in multi-center research and large-scale clinical trials, harmonizing and standardizing laboratory reference values across hospital networks is critical [10]. Ultimately, while CRP is a widely available, cost-effective, and highly practical marker for resource-limited settings, its non-specific nature means it can be influenced by concurrent inflammatory conditions. Consequently, current clinical consensus dictates that CRP should not be interpreted in isolation; instead, it should be integrated into a multimodal diagnostic framework alongside alternative biomarkers, comprehensive clinical evaluations, and radiological findings to optimize predictive accuracy.

Conclusion

In conclusion, the findings from this review show a consistent trend that C-reactive protein (CRP) is a reliable and practical biomarker to be used for predicting the severity of COVID-19 outcomes. Elevation of CRP levels was often strongly associated with disease progression, respiratory complications, ICU admission and mortality when viewed from diverse populations and study designs. CRP also showed their value as an early indicator of a worsening disease that often rises before radiological changes appear, and CRP's usefulness is further supported when making comparisons with other inflammatory markers. Furthermore, CRP-derived ratios like the CRP/albumin ratio and the CRP/lymphocytes ratio provided additional prognostic value. Although CRP alone should not be used as a sole indicator of severity, the accessibility, low cost and strong association with adverse outcomes make it an important tool for early risk assessment and clinical decision making. For future research, it is recommended that researchers should focus on standardising CRP measurement, validating the cut-off value and integrating CRP with other biomarkers to increase its predictive accuracy.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors received no any financial support for this publication.

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