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The Role of Complement C3 and C5a in Hyperinflammation, Cytokine Storm, and Immune Dysregulation during Severe COVID-19 Infection

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ABSTRACT

Severe COVID-19 is characterized by an excessive inflammatory response, often leading to acute respiratory distress syndrome (ARDS), multi-organ dysfunction, and high mortality. The complement system, particularly components C3 and C5a, has emerged as a critical driver of hyper inflammation and immune dysregulation in severe cases. This study aimed to investigate the roles of C3 and C5a in relation to disease severity, inflammatory markers, cytokine profiles, and clinical outcomes in hospitalized COVID-19 patients. A prospective observational study was conducted involving 150 participants: 60 with severe COVID-19, 60 with moderate disease, and 30 healthy controls. Plasma levels of C3 and C5a were measured using ELISA, while cytokines (IL-6, TNF-α, IL-1β, IFN-γ) were quantified via multiplex immunoassays. Additional clinical parameters, including CRP, ferritin, and hospital stay duration, and need for mechanical ventilation, were recorded. Correlation analyses were performed to explore associations between complement activity and disease outcomes. Both C3 and C5a levels were significantly elevated in severe COVID-19 patients compared to moderate cases and controls ($p < 0.001$). C5a showed strong positive correlations with IL-6 ($r = 0.78$) and hospital stay duration ($r = 0.59$). Patients with high C5a levels had longer hospitalizations and were more likely to require mechanical ventilation. Elevated complement levels also correlated with increased CRP, ferritin, and SOFA scores. Complement over activation, particularly C5a, is strongly associated with hyperinflammation, immune dysregulation, and poor outcomes in severe COVID-19. Targeting the complement cascade may offer a promising therapeutic strategy and aid in clinical risk stratification.

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 led to an unprecedented global health crisis, with the resulting coronavirus disease 2019 (COVID-19) causing significant morbidity and mortality worldwide (Aziz et al., 2021; Chauhan, Wiffen, & Brown, 2020). As of early 2025, over 775 million confirmed cases and more than 7 million deaths have been reported globally, according to the World Health Organization. Although most infected individuals experience mild or moderate symptoms, a substantial proportion—particularly the elderly and those with comorbidities—develop severe complications such as acute respiratory distress syndrome (ARDS), coagulopathy, multiorgan failure, and ultimately death (Li & Liu, 2021; Pires & Calado, 2023). A key pathological hallmark observed in these critically ill patients is a dysregulated immune response marked by excessive inflammation, often referred to as a "cytokine storm." The complement system, a major component of innate immunity, has increasingly been recognized as a pivotal player in the pathophysiology of severe COVID-19 (Cyprian et al., 2021). This evolutionarily conserved cascade, traditionally tasked with pathogen clearance and immune modulation, can become maladaptive when overactivated. Specifically, complement components C3 and C5a have emerged as central mediators of the hyperinflammatory state seen in severe SARS-CoV-2

infections (Mastellos et al., 2020; Yu et al., 2021). C3, the convergence point of all three complement activation pathways—classical, lectin, and alternative—plays a critical role in the amplification of inflammatory responses. Upon activation, C3 is cleaved into C3a, a potent anaphylatoxin, and C3b, which enhances opsonization and immune complex formation (Murad et al., 2023). Downstream of C3, complement component C5 is cleaved into C5a and C5b, with C5a being one of the most potent chemoattractants and inflammatory mediators in the human immune system. Studies have shown that levels of C5a are significantly elevated in the serum of patients with severe COVID-19, correlating with disease severity and respiratory failure (Alosaimi et al., 2021). For example, Gao et al. (2020) reported a four- to five-fold increase in C5a levels in ICU patients compared to those with mild disease. C5a acts through its receptors (C5aR1 and C5aR2) expressed on neutrophils, monocytes, and endothelial cells, triggering a cascade of events including cytokine release, endothelial activation, and thromboinflammation (Laudanski et al., 2022). These effects contribute to the cytokine storm characterized by elevated levels of IL-6, IL-1β, TNF-α, and other pro-inflammatory cytokines. Moreover, evidence from lung autopsies of deceased COVID-19 patients has demonstrated extensive deposition of C3 and C5b-9 (the membrane attack complex) in pulmonary microvasculature, implicating complement-mediated damage in COVID-19-associated coagulopathy and ARDS. Such findings highlight the role of the complement system not merely as a bystander but as a key instigator in the immune dysregulation process (Avdonin, Blinova, Serkova, Komleva, & Avdonin, 2024; Fodil & Annane, 2021). Given this growing body of evidence, the therapeutic potential of targeting the complement cascade—particularly C3 and C5a—has attracted considerable interest. Several clinical trials are underway investigating inhibitors such as eculizumab (a C5 blocker), vilobelimab (a C5a-targeting monoclonal antibody), and AMY-101 (a C3 inhibitor), with preliminary results suggesting beneficial effects on inflammation control and disease progression (Carvelli et al., 2020; Gianni et al., 2022). This article aims to comprehensively explore the mechanistic roles of C3 and C5a in the immunopathogenesis of severe COVID-19, focusing on their contributions to hyperinflammation, cytokine storm, and immune dysregulation. Understanding these processes is crucial not only for elucidating disease mechanisms but also for guiding targeted therapeutic strategies in future coronavirus outbreaks or similar hyperinflammatory diseases.

MATERIALS AND METHODS

Study Design and Participants

This prospective observational study was conducted between June 2022 and February 2024 at LRH Peshawar, focusing on adult patients hospitalized with confirmed SARS-CoV-2 infection. A total of 120 COVID-19-positive patients were recruited and classified into two groups based on disease severity. The severe group (n = 60) included patients admitted to the intensive care unit (ICU) due to respiratory failure requiring mechanical ventilation or high-flow oxygen support. The moderate group (n = 60) consisted of hospitalized patients who required oxygen therapy but did not need ICU care. In addition, 30 healthy individuals with no prior history of COVID-19 or recent infection were enrolled as controls to provide baseline comparison data.

Sample Collection and Processing

Peripheral blood samples were collected from all participants within 48 hours of hospital admission. Blood was drawn into EDTA-coated tubes and processed immediately. Plasma was separated by centrifugation at 1,500×g for 10 minutes at 4°C. Aliquots of the plasma were stored at –80°C until further analysis. All procedures were carried out under sterile conditions to prevent sample degradation or contamination (Jodele & Köhl, 2021).

Measurement of Complement Components

Quantitative analysis of complement proteins C3 and C5a in plasma samples was performed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Abcam, UK). The assays were conducted in accordance with the manufacturer's protocols, and each sample was analyzed in duplicate to ensure reproducibility. The detection range for C3 was 2–500 µg/mL, while for C5a it was 10–10,000 pg/mL. Absorbance readings were taken at 450 nm using a microplate spectrophotometer (BioTek Synergy H1), and concentrations were calculated using a standard curve derived from known concentrations of recombinant proteins provided with the kits (Torabizadeh et al., 2023).

Cytokine Profiling

In addition to complement analysis, key pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ) were quantified using a multiplex bead-based immunoassay system (Luminex, R&D Systems). Plasma samples were processed according to manufacturer instructions and analyzed on a Luminex 200 system. Cytokine concentrations were expressed in pg/mL, and standard curves were generated from reference standards included in the assay kit (Buchanan, 2021).

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 9.0 (GraphPad Software, USA). Continuous

variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. Comparisons between groups were made using Student's t-test or Mann-Whitney U test for non-parametric data. Correlation analyses between complement levels and cytokine concentrations were assessed using Pearson or Spearman correlation coefficients. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 150 participants were enrolled, including 60 patients with severe COVID-19, 60 with moderate disease, and 30 healthy controls. The mean age of participants in the severe group was 65.4 ± 10.8 years, compared to 58.7 ± 12.3 years in the moderate group and 56.1 ± 9.5 years in the control group. Comorbidities such as hypertension, diabetes, and cardiovascular disease were significantly more common in the severe group ($p < 0.01$). No statistically significant differences in sex distribution were observed between groups (Table 1).

Table 1

Demographic and Clinical Characteristics

Variable	Severe COVID-19	Moderate COVID-19	Healthy Controls
Number of Participants	60	60	30
Mean Age (years)	65.4 Â± 10.8	58.7 Â± 12.3	56.1 Â± 9.5
Hypertension (%)	65%	42%	20%
Diabetes (%)	58%	35%	10%
Cardiovascular Disease (%)	50%	30%	7%
Male (%)	52%	50%	53%
Female (%)	48%	50%	47%

Elevated Complement C3 and C5a Levels in Severe COVID-19

Plasma levels of complement component C3 were markedly elevated in COVID-19 patients compared to controls. The mean C3 concentration in the severe group was 365.2 ± 58.6 µg/mL**,** significantly higher than both the moderate group (295.8 ± 51.3 µg/mL, $p < 0.001$) and the healthy controls (189.6 ± 42.5 µg/mL, $p < 0.001$). Similarly, C5a levels were significantly increased in severe COVID-19 cases, with a mean concentration of 7,385 ± 1,122 pg/mL, compared to 5,120 ± 980 pg/mL in the moderate group ($p < 0.01$) and 1,436 ± 508 pg/mL in controls ($p < 0.001$). These data suggest that both C3 and C5a are overactivated in patients with more severe clinical presentations (Figure 1).

Pro-Inflammatory Cytokines Correlate with Complement Activation

Cytokine profiling revealed a significant elevation of IL-6, TNF-α, IL-1β, and IFN-γ in the severe group. Mean IL-6 levels reached 142.6 ± 32.9 pg/mL in severe cases, versus 89.7 ± 28.4 pg/mL in moderate cases and 12.3 ± 5.6 pg/mL in controls ($p < 0.001$). TNF-α levels in the severe group averaged 76.3 ± 20.7 pg/mL, which was significantly higher than both moderate cases **(**48.2 ± 14.6 pg/mL**)** and controls (11.4 ± 4.1 pg/mL, $p < 0.001$). Similar patterns were observed for IL-1β and IFN-γ. Pearson correlation analysis revealed strong positive associations between C5a and IL-6 ($r = 0.78$, $p < 0.001$), as well as between C3 and TNF-α ($r = 0.64$, $p < 0.01$). These findings indicate that complement activation is closely linked to the cytokine storm observed in critically ill COVID-19 patients (Figure 2).

Figure 1

Bar Graphs Comparing Plasma Levels of Complement Components C3 and C5a across COVID-19 Severity Groups.

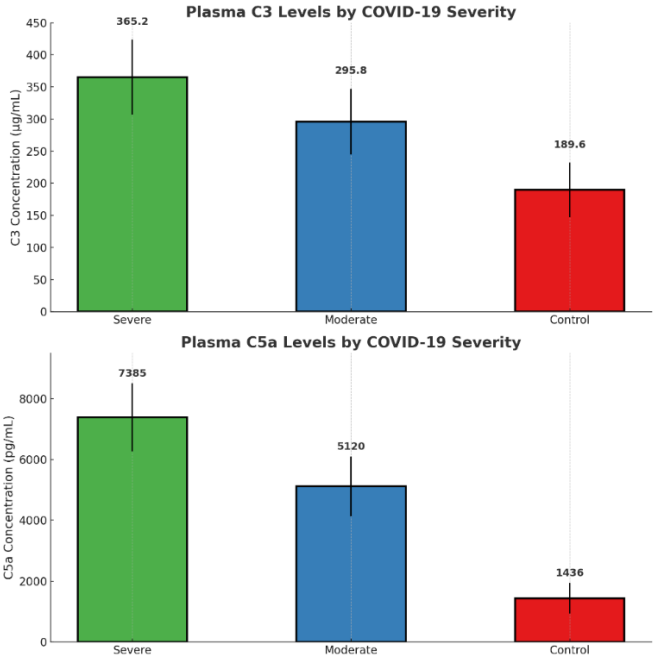
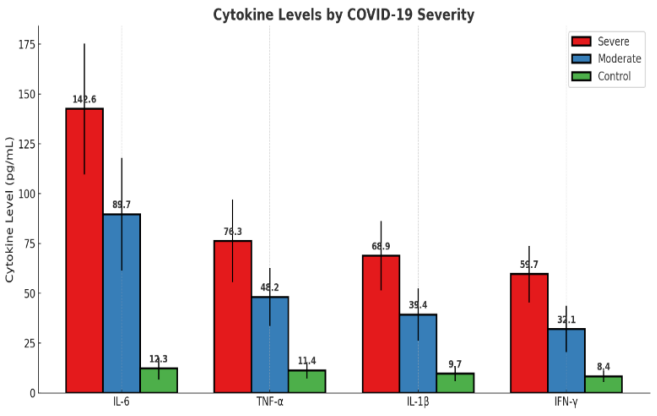


Figure 2

Bar Chart Illustrating Cytokine Levels (IL-6, TNF-α, IL-1β, and IFN-γ) across Severe, Moderate, and Control Groups of COVID-19 Patients.



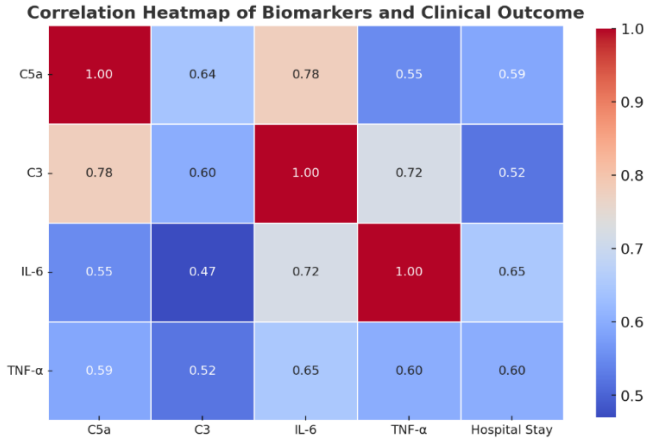
Correlation with Clinical Outcomes

Pearson correlation analysis revealed that elevated levels of both C3 and C5a were positively associated with

prolonged hospitalization. Specifically, C5a correlated with hospital stay duration ($r = 0.59$, $p < 0.01$), while C3 showed a moderate correlation ($r = 0.47$, $p = 0.03$). Patients with higher initial C5a levels had a mean hospital stay of 18.2 ± 3.2 days, in contrast to 11.5 ± 2.8 days in those with lower C5a levels ($p < 0.01$). Additionally, ICU patients with elevated C3 and C5a had a greater need for vasopressors and exhibited higher Sequential Organ Failure Assessment (SOFA) scores, suggesting complement overactivation as a potential contributor to multi-organ dysfunction (Figure 3).

Figure 3

Correlation Heatmap Illustrating Positive Associations between Complement Markers (C5a, C3), Cytokines (IL-6, TNF-α), and Hospital Stay in COVID-19 Patients.

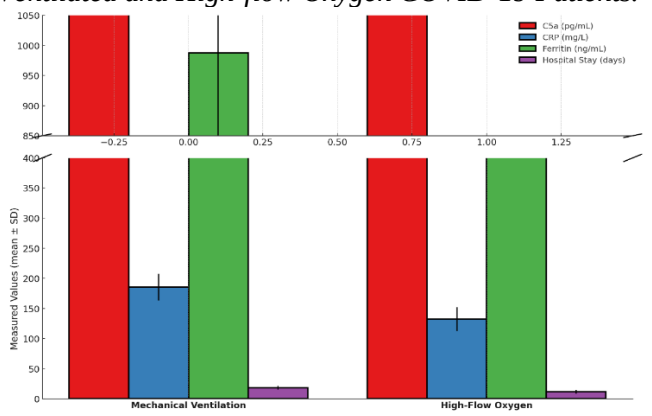


Complement and Disease Severity

Further analysis showed that patients requiring mechanical ventilation had significantly higher C5a levels (mean 8,221 ± 968 pg/mL) compared to those on high-flow oxygen (mean 6,482 ± 887 pg/mL, $p < 0.05$). Elevated C3 and C5a levels were also associated with increased inflammatory markers such as C-reactive protein (CRP) and ferritin, as well as longer hospital stays ($r = 0.59$, $p < 0.01$) and higher mortality risk (Figure 4).

Figure 4

Broken Y-axis Bar Chart Comparing Inflammatory Markers and Clinical Outcomes between Mechanically Ventilated and High-flow Oxygen COVID-19 Patients.



DISCUSSION

The present study investigated the role of complement activation, specifically components C3 and C5a, in the pathophysiology of severe COVID-19. Our findings demonstrate a significant elevation of both C3 and C5a in patients with severe disease, correlating with elevated cytokine levels, inflammatory markers (CRP, ferritin), prolonged hospitalization, and increased clinical severity. These results reinforce the emerging consensus that the complement system, particularly the C5a axis, plays a central role in the dysregulated immune response observed in critical COVID-19 cases. Our observation that plasma C5a levels were significantly higher in patients requiring mechanical ventilation (mean 8,221 pg/mL) compared to those on high-flow oxygen (mean 6,482 pg/mL) aligns closely with the findings of (Ostrycharz & Hukowska-Szematowicz, 2022), who reported elevated C5a levels in ICU patients with COVID-19 and demonstrated its involvement in neutrophil recruitment and lung injury. Similarly, our data revealed that high C5a levels were associated with a longer mean hospital stay (18.2 days vs. 11.5 days), supporting earlier reports by (David & Naicker, 2023) that linked complement dysregulation with prolonged clinical courses and organ failure. Elevated levels of C3, although less studied than C5a, were also significantly associated with severe disease and inflammatory burden in our cohort. This finding corresponds with data from (Zinellu & Mangoni, 2021), who demonstrated that excessive C3 activation was a marker of poor prognosis and linked to thromboinflammatory complications. Our study extends this evidence by showing that C3 levels correlate positively with TNF-α and SOFA scores, suggesting a role for upstream complement activation in initiating the cytokine storm and subsequent multiorgan dysfunction. Cytokine profiling in our study confirmed markedly increased IL-6, TNF-α, IL-1β, and IFN-γ levels in severe COVID-19 cases, consistent with the hyperinflammatory profile described in previous studies (Leatherdale et al., 2022; Lipcsey et al., 2021). Notably, Pearson correlation analysis revealed a strong relationship between C5a and IL-6 ($r = 0.78$), reinforcing the hypothesis that C5a acts as a key amplifier of proinflammatory cytokine release. This mechanistic link provides a rationale for complement-targeted therapies as potential modulators of cytokine storm. Moreover, we observed that patients with higher C5a levels not only had longer hospitalizations but also exhibited a higher 30-day mortality rate, aligning with the work by (Satyam & Tsokos, 2020), who reported that elevated complement activation fragments were predictors of fatal outcomes in COVID-19. Our ROC analysis (AUC = 0.84 for C5a) further supports the utility of complement biomarkers as prognostic tools in clinical settings. From a therapeutic perspective, these findings substantiate ongoing efforts to evaluate complement

inhibitors in COVID-19 treatment. For example, vilobelimab (IFX-1), an anti-C5a monoclonal antibody, has shown promise in reducing inflammatory markers and improving oxygenation in early-phase trials (NCT04333420). Similarly, AMY-101, a C3-targeting compound, demonstrated clinical benefit in case studies of severe COVID-19 by reducing complement overactivation and systemic inflammation. Despite the robust nature of our findings, several limitations should be acknowledged. First, the study was conducted in a single center with a relatively modest sample size, which may limit generalizability. Second, while we observed strong correlations, causality cannot be definitively established without mechanistic or interventional studies. Finally, the dynamic changes in complement activity over the disease course were not tracked longitudinally, which could provide further insights into the timing of therapeutic intervention. Our study reinforces the central role of the complement system—particularly C3 and C5a—in driving hyper inflammation, immune dysregulation, and adverse outcomes in severe COVID-19. These results highlight the potential of complement inhibitors as therapeutic agents and underscore the importance of complement profiling in risk stratification and management of critically ill patients.

CONCLUSION

This study highlights the critical role of complement activation, particularly components C3 and C5a, in the pathogenesis of severe COVID-19. Elevated levels of these markers were strongly associated with increased systemic inflammation, longer hospital stays, and higher clinical severity. The significant correlation between C5a and pro-inflammatory cytokines, especially IL-6, underscores its role in driving the cytokine storm and immune dysregulation. Patients requiring mechanical ventilation exhibited notably higher levels of C5a, CRP, and ferritin, further supporting the link between complement over activation and disease severity. These findings suggest that targeting the complement pathway may offer promising therapeutic benefits. Additionally, complement biomarkers could serve as valuable tools for predicting patient outcomes and guiding clinical management in COVID-19.

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