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Impact of complement system proteins on the clinical progression of hospitalized patients with COVID-19

Lorena Viana de Andrade[1], Beatriz Vasconcelos[2], Ricardo Khouri[2], Carlos Dornels Freire de Souza[3], Anderson da Costa Armstrong[3] and Rodrigo Feliciano do Carmo[1,3*]

Abstract

Background The complement system is an important defense mechanism against pathogens, including viruses. In COVID-19, evidence suggests that hyperactivation of the complement system can lead to tissue damage and provoke dysregulation of the coagulation cascade, resulting in vascular damage observed in severe COVID-19. There is still little evidence regarding the role of plasma levels of these molecules in the clinical evolution of hospitalized patients with COVID-19.

Methods The study included individuals 18 years of age or older with confirmed diagnosis of COVID-19, admitted to two referral hospitals in the Northeast Region of Brazil between August 2020 and July 2021. Plasma samples were collected within 24 hours of hospital admission. Patients were followed up until discharge, and complications during hospitalization were duly recorded. Plasma levels of the following complement proteins were determined by Luminex: C2, C3, C3b/iC3b, C4, C4b, C5, C5a, MBL, C1q, factor I, factor D, factor B, and factor H. A multivariate logistic regression analysis was used to correct the results according to possible confounding factors.

Results The study included 267 patients (134 critical and 133 severe), with mean ages of 54 and 52 years, respectively. Plasma levels of C2, C5a, factor B, and factor D were significantly higher in patients who required intensive care unit admission, required ventilatory support, developed sepsis, developed cardiorespiratory arrest, or developed acute kidney failure. On the other hand, C4b level was lower in patients who developed complications. Complement proteins were significantly associated with laboratory parameters related to coagulation and kidney function.

Conclusion These findings show that the complement system is associated with COVID-19 complications and laboratory parameters of coagulation and kidney function. These results suggest that these molecules may be potential biomarkers or therapeutic targets in the clinical progression of COVID-19.

Keywords Biomarkers, COVID-19, Innate immunity, Complement system, SARS-CoV-2

*Correspondence:
Rodrigo Feliciano do Carmo
rodrigo.carmo@univasf.edu.br
[1]Postgraduate Program in Biosciences, Federal University of the São Francisco Valley, Petrolina, Brazil
[2]Gonçalo Moniz Institute, Oswaldo Cruz Foundation (Fiocruz), Salvador, Brazil
[3]College of Medicine, Federal University of the São Francisco Valley, Petrolina, Brazil

Background

Since the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were reported in December 2019 in Wuhan, China, there has been a significant expansion in the number of cases worldwide. As of May 1, 2023, more than 753 million cases had been reported worldwide, resulting in more than 6.8 million deaths [1].

The complement system is an important primary immune defense mechanism against viruses, consisting of a proteolysis-based activation cascade composed of more than forty plasma proteins [2]. The complement system can be activated through three different pathways, the classical (CP), the lectin (LP), and the alternative (AP) pathway, all leading to the formation of C3 convertase and, finally, to the formation of the membrane attack complex (MAC) [3]. After recognizing viruses or viral particles, this system performs four main functions: lysis of infected cells or enveloped viruses through the formation of the membrane attack complex (MAC or C5b-9 complex) [4], direct opsonization of viral particles [5], solubilization of antibody-virus complexes [6], and activation of inflammation in the host [7].

Although the main function of the complement system in viral infections is to protect the host from invading viruses, complement overactivation also appears to play a role in the pathogenesis of COVID-19. Indeed, studies have reported that complement activation was associated with greater disease severity, intensive care unit (ICU) admission, and increased mortality [8–16]. Moreover, clinical trials with C5a-targeted complement inhibitors in the treatment of severe cases of COVID-19 have shown promising results [17–19]. Recent data indicate that the functional connection between the complement system, coagulation cascade, and intrinsic complement production by lung cells are involved and may, therefore, be promising new therapeutic targets for disease severity.

Although previous studies have investigated complement system protein levels in COVID-19, they were limited to investigating some individual components in relation to clinical course and susceptibility to infection in small cohorts. In our study, we investigated the association of the components C2, C3, C3b/iC3b, C4, C4b, C5, C5a, MBL, C1q, factor I, factor D, factor B, and factor H with the severity of COVID-19, post-hospitalization complications, and their relationship with laboratory parameters.

Methods

Study design, location, and target population

This is a cross-sectional, analytical study with a quantitative approach. Samples were included from individuals of both sexes, 18 years of age or older, with COVID-19 confirmed by molecular (RT-PCR) or immunological testing, who were hospitalized between August 2020 and July 2021 at the University Hospital of the Universidade Federal do Vale do São Francisco (HU-UNIVASF/EBSERH) and the Field Hospital of the Municipality of Petrolina, both reference centers for the treatment of COVID-19 in the Vale do São Francisco Region, in the city of Petrolina, Pernambuco, located in the Northeast Region of Brazil.

Patients were classified as critical when they developed critical disease, whether pulmonary, with high-flow oxygen therapy, mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, and intubation), septic shock, or damage to any other organ that required ICU admission. Patients who developed pneumonia, required low-flow oxygen, or were admitted to ward beds were classified as severe.

This study received approval from the Ethics Committee of the Hospital das Clínicas of the Federal University of Pernambuco (HC/UFPE) under register number CAAE: 38.196.620.0.0000.8807, and it was conducted in accordance with the provisions of the Declaration of Helsinki and the Good Clinical Practice guidelines.

Sample collection and processing

Biological Material was collected by the nursing service within 24 h of patient admission, by means of vacuum venipuncture in a tube containing EDTA, and subsequently sent to the HU/UNIVASF Clinical Research Laboratory (LAMUPE). After receipt, the samples were processed, separated into blood, serum, and plasma. They were then stored in refrigerators at − 80 °C until the plasma was used.

Complement protein quantification

A multiplex assay (Luminex xMAP), based on technology that uses Magnetic beads, was used to determine plasma levels, by means of a commercially available MILLIPLEX MaP Human Complement Panel 1 and 2 kit (Millipore Corporation, Billerica, MA, USA. Number: HCMP-1MAG-19 K) following manufacturer instructions. Concentrations of complement proteins, including C2, C4b, C5, C5a, MBL, factor D and factor I (panel 1), C1q, C3, C3b/iC3b, C4, factor B and factor H (panel 2), were analyzed on a Luminex 200 system, and median fluorescence intensity (MFI) was obtained.

Statistical analyses

The Shapiro-Wilk test was used to verify whether variable distribution was normal. Continuous variables were compared using the Mann-Whitney test. Pearson's chi-square test was used for categorical variables. Spearman's correlation test was performed to correlate plasma levels and laboratory parameters. Results were presented using a heat Map and network analysis, with strength of correlation coefficients displayed on a color scale. To reduce

the risk of bias, the significant results were adjusted for possible confounding factors using a multivariate Logistic regression model. Data were stored and analyzed using JASP 0.18.3 software. Column graphs were constructed using GraphPad Prism software, version 9.0.

Results

The study included a total of 267 patients: 134 admitted to the ICU and classified as critical and 133 admitted to ward beds and classified as severe. The mean age in the severe group was 52 years; in the critical group it was 54 years ($p = 0.38$). Male sex was more prevalent in both groups, 60.9% in the severe group and 57.5% in the critical group ($p = 0.57$) (Table 1).

In relation to comorbidities, only the occurrence of obesity was significantly different between the groups, with a prevalence of 28.3% in the critical group versus 15.1% in the severe group ($p = 0.009$). After hospitalization, patients were followed up and assessed for their progress. The variables, use of invasive ventilation, cardiopulmonary arrest, sepsis, acute kidney failure, and death were significantly more prevalent in the critical group ($p < 0.0001$, for all comparisons). The mean length of hospital stay was longer in the critical group than in the severe group (15.0 days versus 5.8 days, $p < 0.0001$) (Table 1).

Legend – COPD: chronic obstructive pulmonary disease; SD: standard deviation.

Table 1 Baseline characteristics and clinical evolution of the patients included in the study

	Severe COVID-19 (*N* = 133)	Critical COVID-19 (*N* = 134)	*P* *
Demographic			
Age, years (mean ± SD)	52.4 ± 14.9	54.1 ± 17.2	0.38
Male, n (%)	81 (60.9)	77 (57.5)	0.57
Female, n (%)	52 (39.1)	57 (42.5)	
Comorbidities			
Diabetes mellitus, n (%)	36 (27.2)	49 (36.5)	0.10
Hypertension, n (%)	54 (40.9)	63 (47.0)	0.32
Obesity, n (%)	20 (15.1)	38 (28.3)	0.009
Chronic kidney disease, n (%)	2 (1.5)	6 (4.4)	0.16
Chronic heart disease, n (%)	3 (2.2)	5 (3.7)	0.49
Asthma, n (%)	2 (1.5)	7 (5.2)	0.09
Cancer, n (%)	1 (0.7)	4 (2.9)	0.18
COPD, n (%)	1 (0.7)	4 (2.9)	0.18
Clinical evolution			
Invasive ventilation, n (%)	0	106 (79.1)	< 0.001
Cardiorespiratory arrest, n (%)	0	35 (32.4)	< 0.001
Sepsis, n (%)	0	26 (20.1)	< 0.001
Acute kidney injury, n (%)	0	43 (32.8)	< 0.001
Death, n (%)	0	50 (37.3)	< 0.001
Length of stay, days (mean ± SD)	5.8 ± 6.7	15.0 ± 12.1	< 0.001

Complement system protein levels were assessed from samples collected within 24 h of admission. Critical patients were observed to have higher plasma levels of C2 ($p < 0.0001$), C5a ($p < 0.0001$), C5a/C5 ratio ($p < 0.0001$), and factor B ($p = 0.016$) upon admission, compared to severe patients. On the other hand, levels of C4b ($p = 0.0309$), C4b/C4 ratio ($p = 0.0138$), and C3b/iC3b ($p = 0.018$) were lower in the group of critical patients (Fig. 1). After correction using a multivariate model adjusting for sex, age, and obesity as possible confounders, the components C4b ($p = 0.033$), C4b/C4 ratio ($p = 0.043$), C2 ($p = 0.031$), C5a ($p = 0.002$), C5a/C5 ratio ($p < 0.001$), and factor B ($p = 0.034$) remained statistically significant. No significant difference was observed for the other components.

Regarding the outcome, a significant association was observed between higher levels of C2 and factor D and the occurrence of death ($p < 0.0001$, $p = 0.0016$, respectively), while C3 and C3b/iC3b levels were lower in deaths ($p = 0.0458$, $p = 0.0488$, respectively) (Fig. 2). After correction, no component remained statistically significant.

Furthermore, patients who required invasive ventilation during hospitalization were observed to have higher levels of C2 ($p < 0.0001$), C5a ($p < 0.0001$), C5a/C5 ratio ($p = 0.0002$), C1q ($p = 0.0188$), and factor B ($p = 0.0066$) upon admission. The C4b/C4 ratio levels ($p = 0.0075$) were significantly lower in these patients (Fig. 3). After correction, the C4b/C4 ratio ($p = 0.019$), C5a ($p < 0.001$), C5a/C5 ratio ($p < 0.001$) and factor B ($p = 0.005$) remained significant.

Regarding the occurrence of sepsis during hospitalization, higher levels of C2 ($p < 0.0001$), C5a ($p = 0.0092$), and C1q ($p = 0.0175$) were observed in affected patients. On the other hand, levels of C3 ($p = 0.0217$) and C3b/iC3b ($p = 0.0120$) were decreased when compared to patients who did not develop sepsis (Fig. 4). After correction, no component remained statistically significant.

Levels of C2 component ($p < 0.0001$) and factor D ($p = 0.0060$) were significantly higher in patients who developed cardiorespiratory arrest during hospitalization. There was no significant association for the other components (Fig. 5). After correction, factor D ($p = 0,019$) remained significant.

When we assessed the relationship between complement system components and the occurrence of acute kidney failure during hospitalization, we observed a significant association between higher levels of C2 ($p < 0.0001$), C5a ($p = 0.0447$), C1q ($p = 0.0373$), and factor D ($p = 0.0280$). Levels of C4b ($p = 0.0022$) and C4b/C4 ratio ($p = 0.0016$) were lower in patients who developed acute kidney failure (Fig. 6). After correction, C4b ($p = 0.016$), C4b/C4 ratio ($p = 0.022$), C2 ($p = 0.026$) and C5a ($p = 0.012$) remained significant.

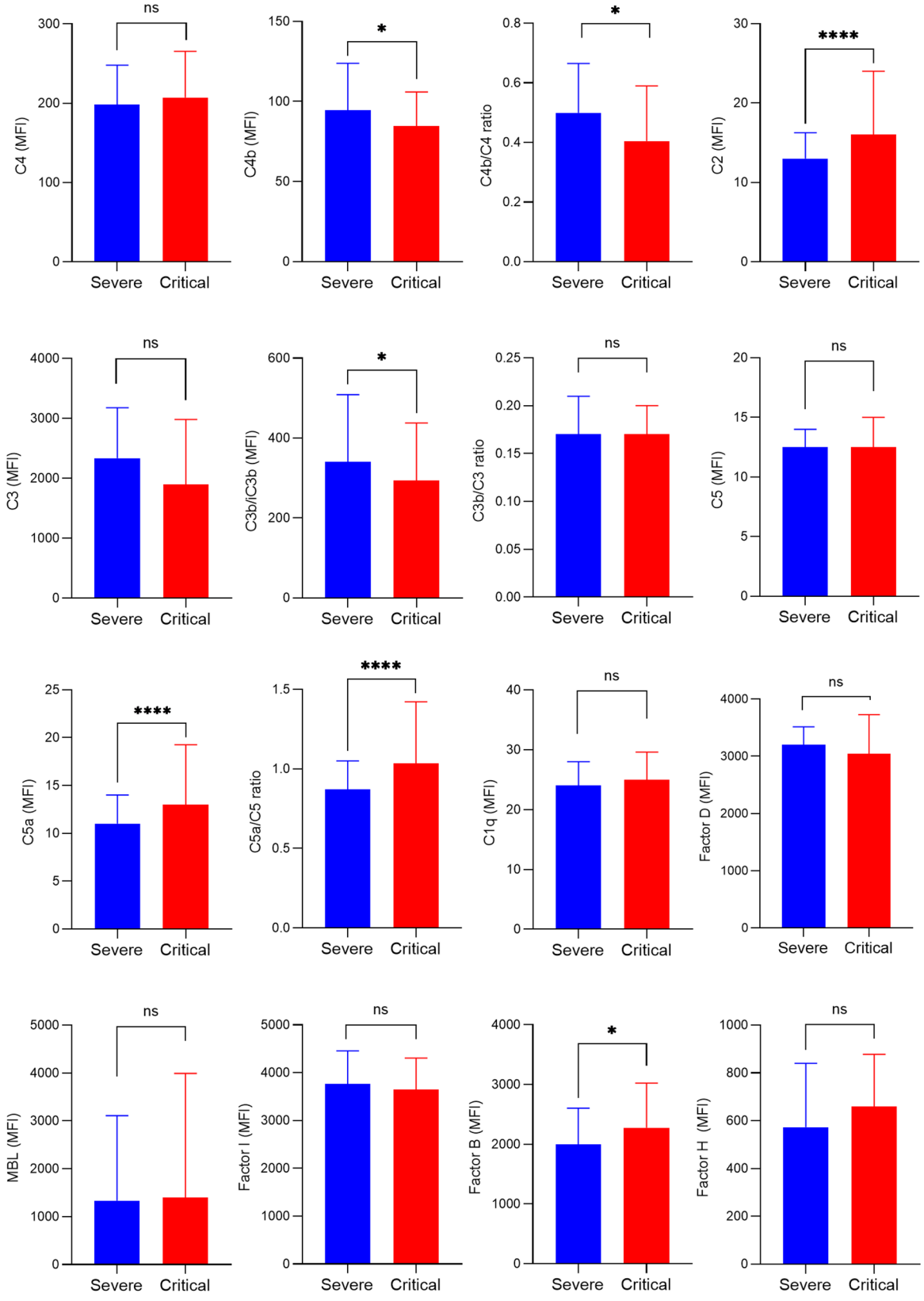

Fig. 1 Association of plasma levels of complement proteins with the severity of COVID-19. Data are shown as median and interquartile range. Statistical significance was determined using Mann-Whitney test. MFI: median fluorescence intensity; ns: not significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

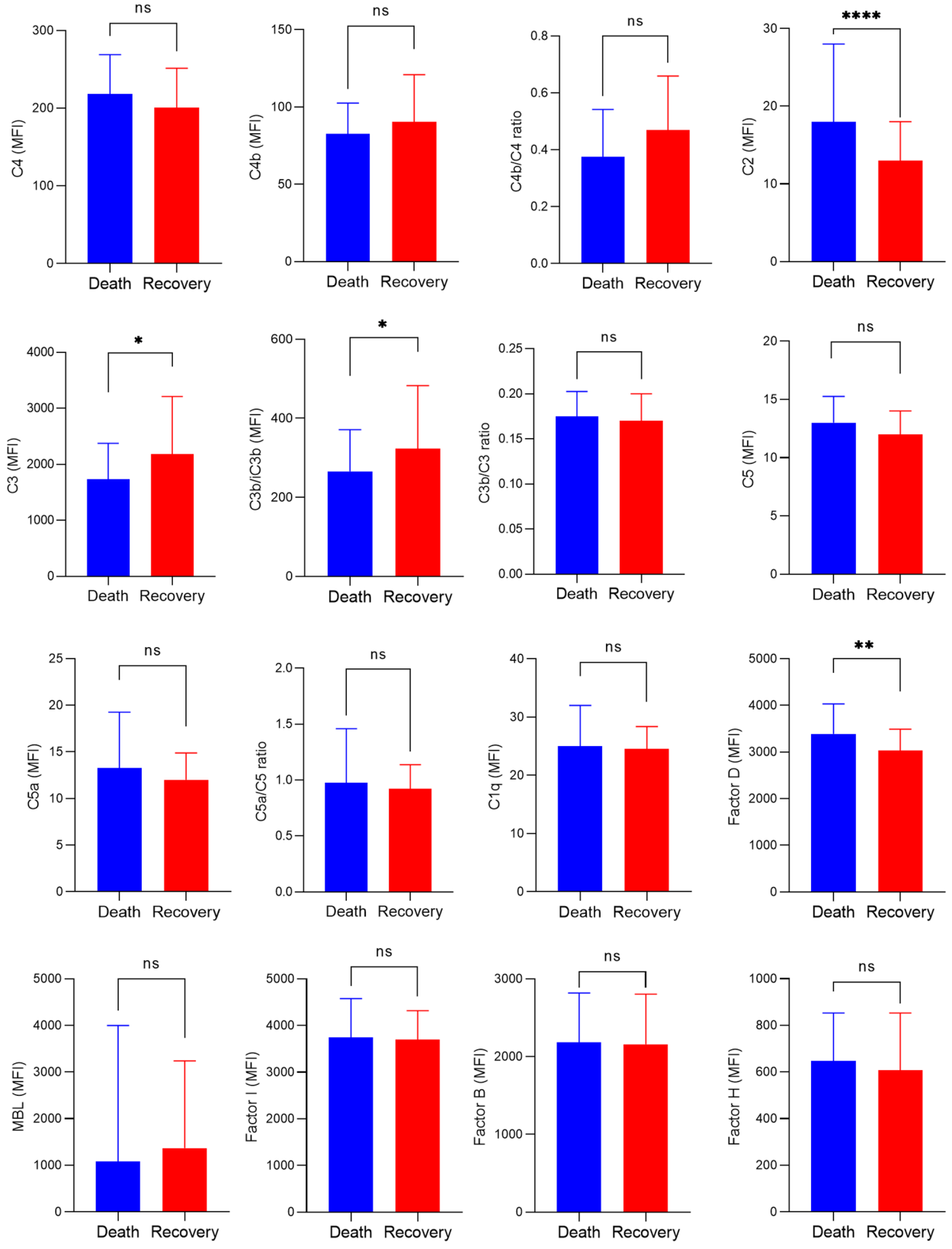

Fig. 2 Association of plasma levels of complement proteins with the outcome of COVID-19. Data are shown as median and interquartile range. Statistical significance was determined using Mann-Whitney test. MFI: median fluorescence intensity; ns: not significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

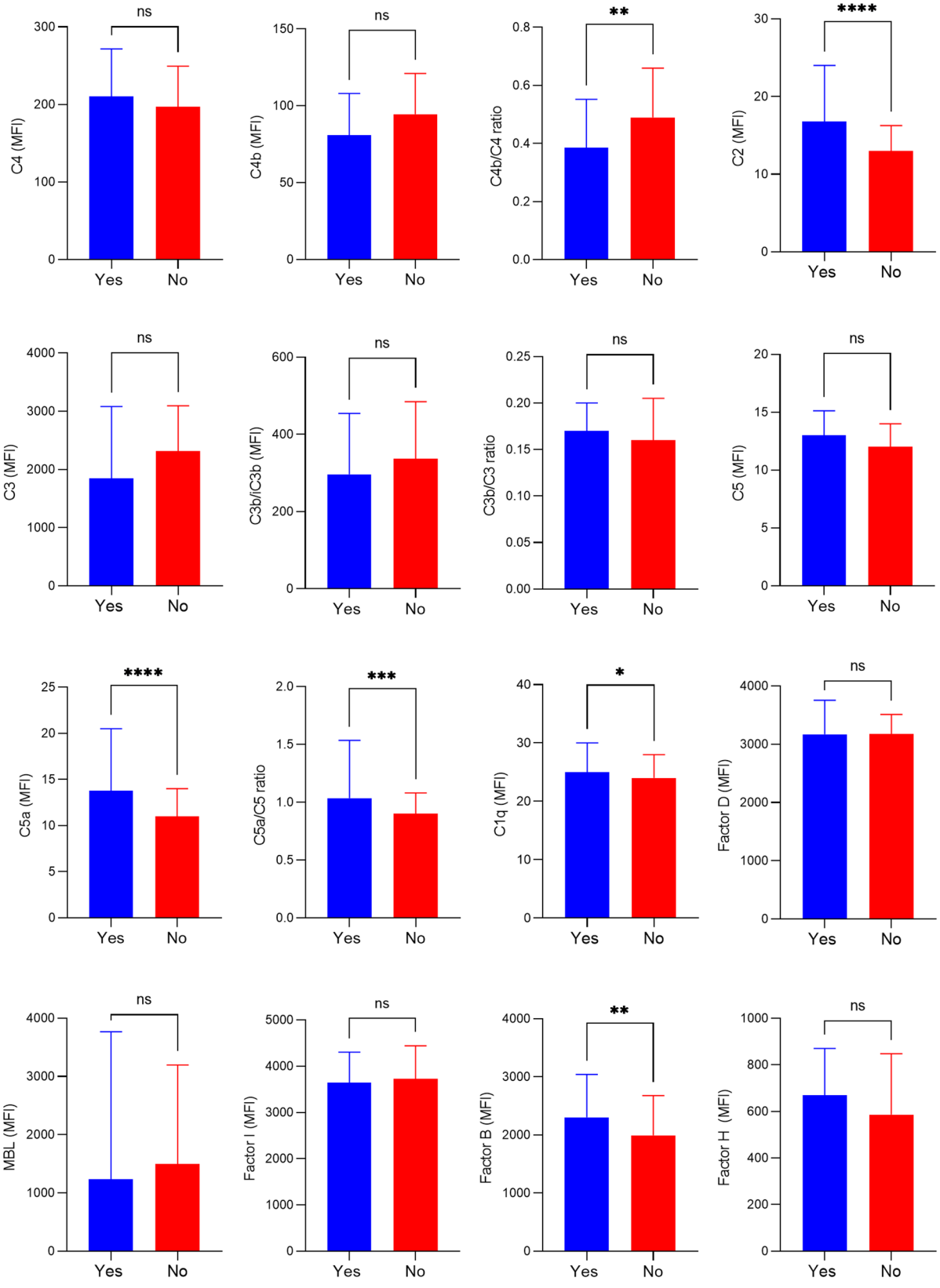

Fig. 3 Association of plasma levels of complement proteins with the need for invasive ventilatory support in patients with COVID-19. Data are shown as median and interquartile range. Statistical significance was determined using Mann-Whitney test. MFI: median fluorescence intensity; ns: not significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

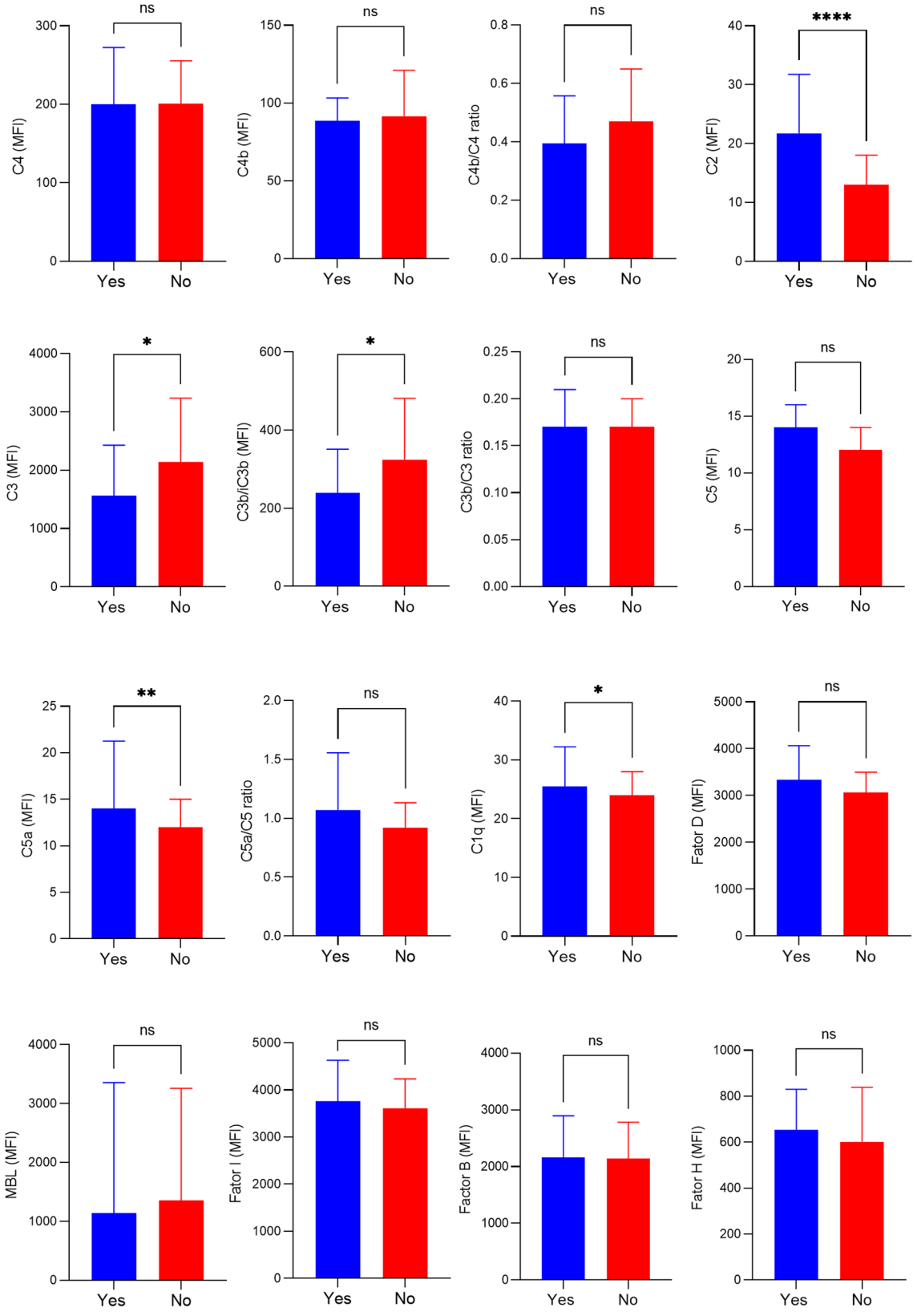

Fig. 4 Association of plasma levels of complement proteins with the occurrence of sepsis in patients with COVID-19. Data are shown as median and interquartile range. Statistical significance was determined using Mann-Whitney test. MFI: median fluorescence intensity; ns: not significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

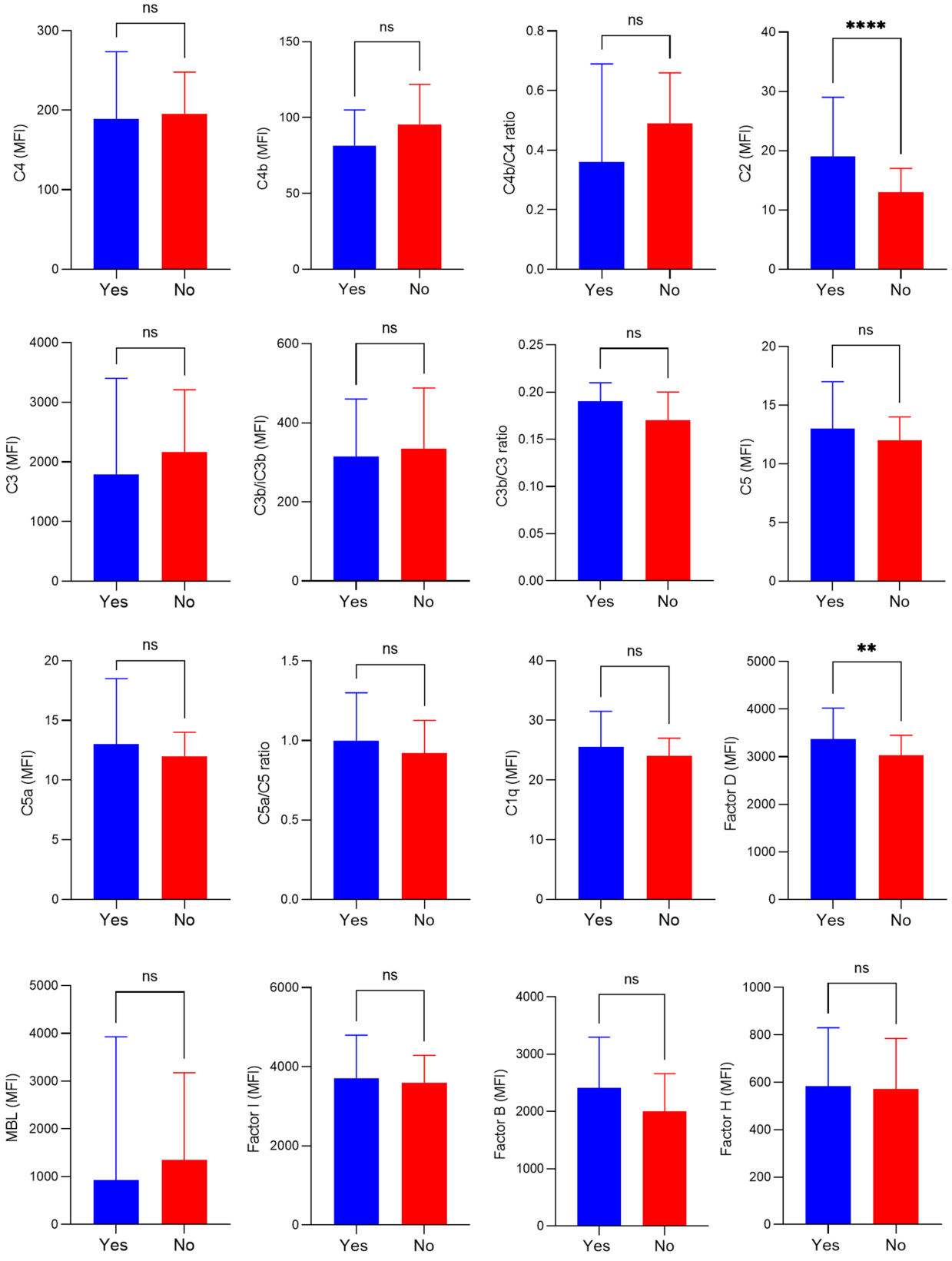

Fig. 5 Association of plasma levels of complement proteins with the occurrence of cardiorespiratory arrest in patients with COVID-19. Data are shown as median and interquartile range. Statistical significance was determined using Mann-Whitney test. MFI: median fluorescence intensity; ns: not significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

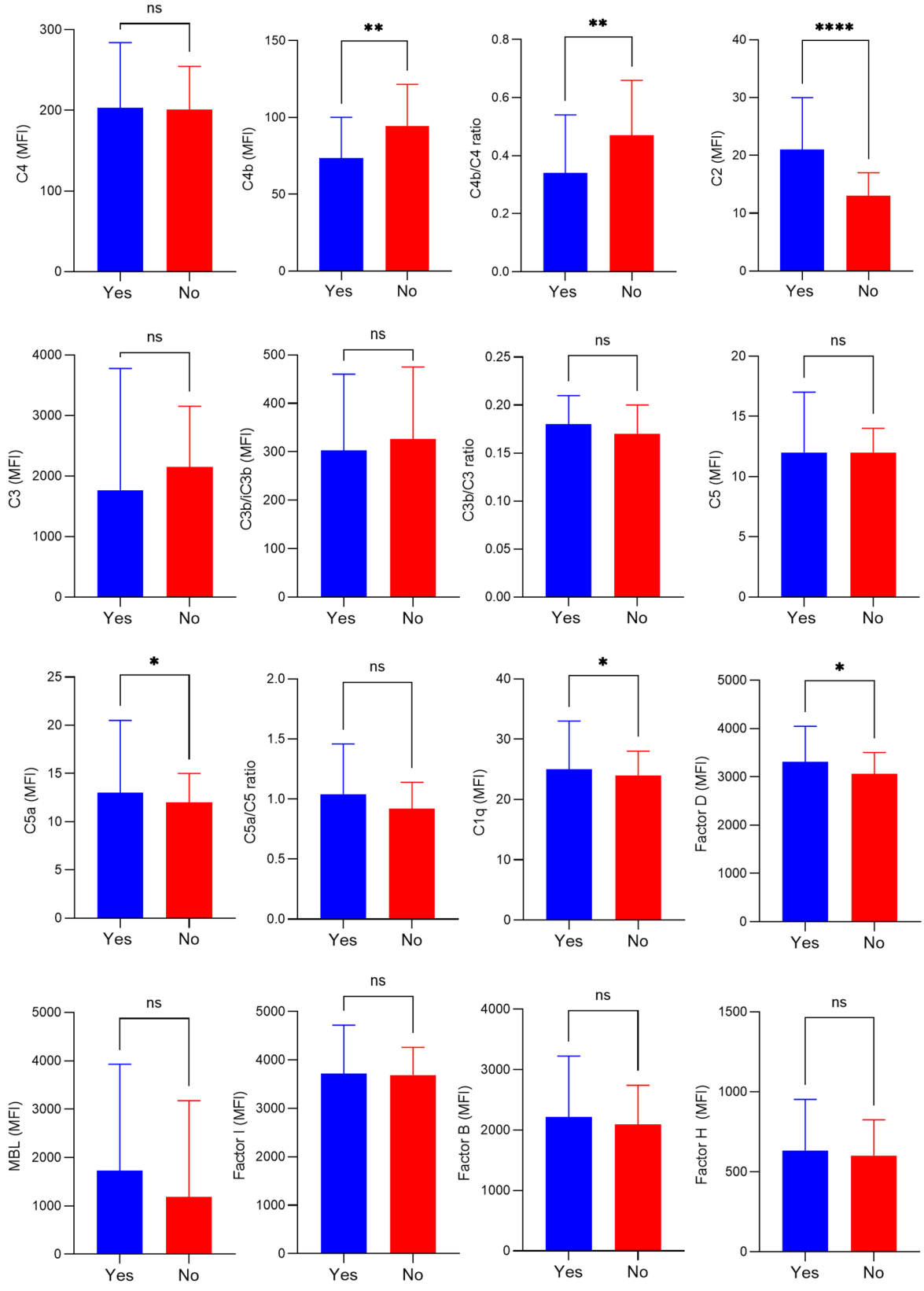

Fig. 6 Association of plasma levels of complement proteins with the occurrence of acute kidney injury in patients with COVID-19. Data are shown as median and interquartile range. Statistical significance was determined using Mann-Whitney test. MFI: median fluorescence intensity; ns: not significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

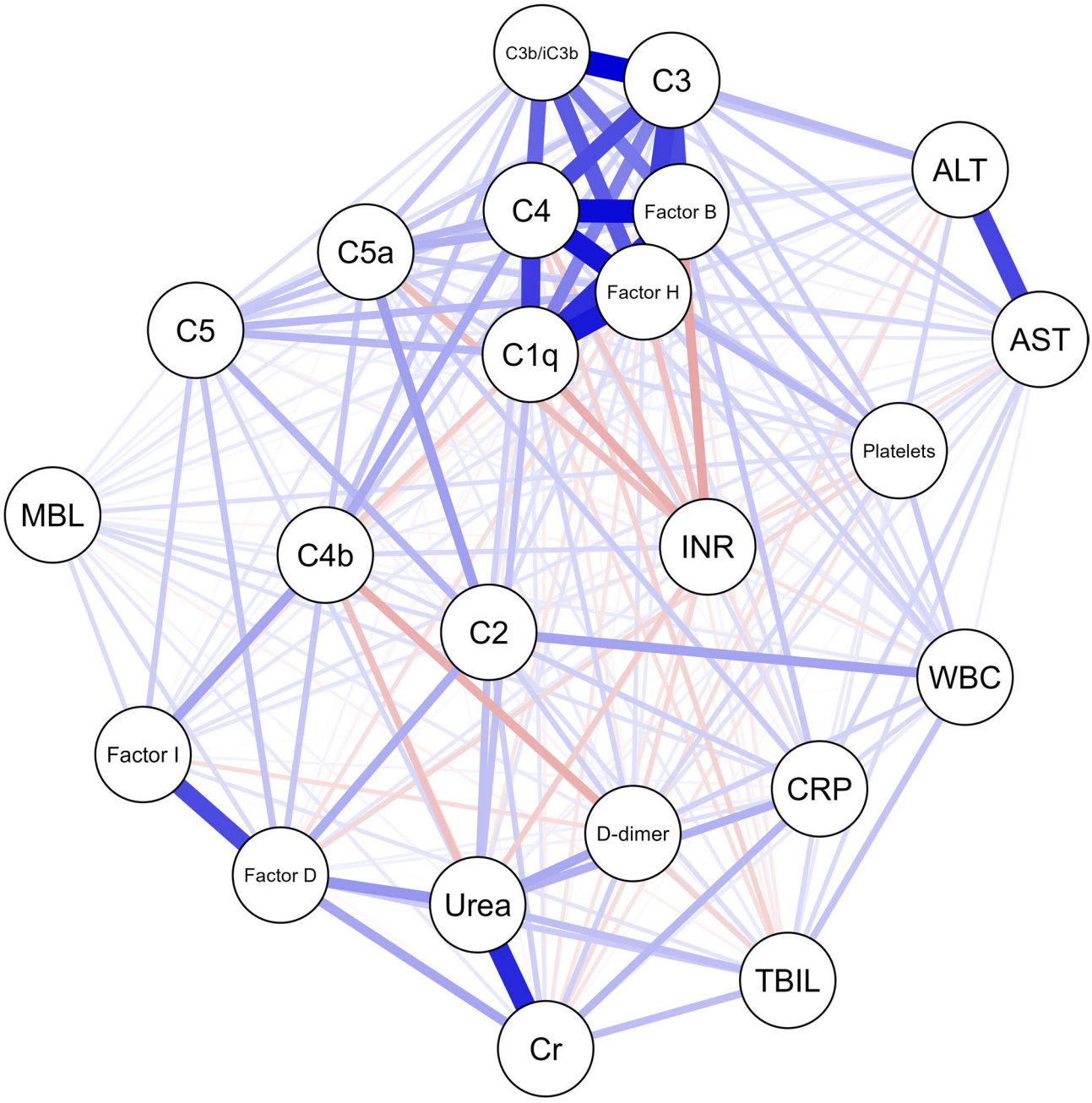

Fig. 7 Network analysis of complement proteins and laboratory parameters in patients hospitalized with COVID-19. Blue lines indicate a positive correlation. Red lines indicate a negative correlation. The thickness of the lines is proportional to the strength of the correlation. ALT: alanine transaminase; AST: aspartate transaminase; Cr: creatinine; CRP: C-reactive protein; INR: international normalized ratio; MBL: mannose-binding lectin; TBIL: total bilirubin, WBC: white blood cell

Finally, regarding the strength of correlation coefficients on network analysis together with the heat map, a correlation was demonstrated between platelet count and levels of MBL, C3, C3b, C4, factor B, factor D, and factor H. In contrast, other coagulation markers such as INR, prothrombin time, and APTT were inversely correlated with the proteins C2, C5a, C1q, C4, in addition to factors B and H. A significant correlation was also observed for creatinine and urea, which are markers of kidney failure, with C2, C5, and factor D (Fig. 7 and Supplementary Fig. 1).

Discussion

Our results suggest that complement proteins play an important role in the clinical course of COVID-19 in hospitalized patients. These findings reinforce previous

evidence found in European populations and bring new data regarding the dynamics of these proteins and the risk of complications during hospitalization, including outcome, risk of invasive ventilatory support, sepsis, kidney failure, and cardiopulmonary arrest.

The complement system plays a complex role in COVID-19. Previous studies have demonstrated activation of the complement system by all three pathways in lung and kidney tissue samples from patients with COVID-19 [10]. In vitro experiments have shown that lectin pathway recognition molecules, such as MBL, FCN-2, and CL-11, bind to SARS-CoV-2 S and N proteins, leading to activation of the lectin pathway and deposition of C3b and C4b [20]. Genetic polymorphisms in the *MBL2* gene have also been associated with COVID-19 severity [21, 22]. Moreover, the spike protein can directly deregulate the alternative pathway by binding to heparan sulfate and competing with factor H, a negative regulator of complement activity [23–25].

Thus, while the complement system plays a crucial role in combating SARS-CoV-2, especially early in infection, it may also have a deleterious effect by exacerbating inflammation and interacting with the coagulation cascade. This can lead to tissue damage, vascular changes, and thrombosis observed in severe COVID-19 cases [26]. The mechanism driving the transition of the complement system from protective to harmful remains unclear but may involve the interplay between local and systemic complement activation induced by the virus.

In this study, we observed that plasma levels of C2, C5a, factor B, and factor D were significantly higher in critical patients, regardless of the severity parameter used, including ICU admission, invasive ventilatory support, cardiopulmonary arrest, and kidney failure. Our findings are consistent with Ma et al. (2021), who also found significant associations between levels of C5a, factor D, factor B, and adverse outcomes in hospitalized COVID-19 patients [27].

Several previous studies have explored the relationship between complement components and clinical parameters of COVID-19 [28–41]. Although some contradictory results have been reported–potentially due to differences in study design, sample size, sample types (serum, EDTA plasma, citrate), or quantification methods–there is consistent evidence linking elevated C5a levels to disease severity. As a potent anaphylatoxin, C5a promotes the recruitment of neutrophils, monocytes, and other immune cells, contributing to an uncontrolled inflammatory response characterized by excessive cytokine release, tissue damage, endothelialitis, and microthrombosis [43]. In line with this, clinical trials using anti-C5a antibodies have demonstrated improvements in patients outcomes, including reduced mortality risk [17–19].

Our results also indicate high levels of factor B and factor D in severe clinical conditions. Transcriptome analyses have shown that factor B is one of the complement genes most strongly induced following SARS-CoV-2 infection, and inhibition of factor B significantly reduced C3a production in vitro [29]. These observations, along with evidence that SARS-CoV-2 activates the alternative pathway through interaction with cell surface heparan sulfate [44], underscore the importance of the alternative pathway in COVID-19 pathogenesis. Elevated levels of factor D have also been associated with poor outcomes, including death [27], and reductions in properdin, a key alternative pathway regulator, were noted in mechanically ventilated patients [30], reinforcing the alternative pathway's critical role [34].

In addition to the alternative pathway, our study revealed elevated C1q levels in patients requiring invasive ventilatory support, those who developed sepsis, and those with acute kidney failure. Although this association did not remain statistically significant in multivariate analysis, previous studies, such as Castanha et al. (2022), reported that C1q levels were significantly elevated in severe cases and correlated with higher IgG titers, greater complement activation, and increased disease severity [36].

C1q, a key initiator of the classical pathway, is activated by antigen-antibody complexes. The intense inflammatory response and immune complex formation in critically ill patients could stimulate C1q production by inflammatory cells, potentially explaining the elevated C2 levels observed in our study. The components C2 and C4 are consumed during activation of the classical and lectin pathways, and compensatory hepatic production may occur to replenish depleted levels. However, findings regarding C1q are conflicting. Alosaimi et al. (2021) found no significant difference in C1q levels between critical and mild COVID-19 cases in a small cohort in Saudi Arabia [31], whereas a British cohort study observed reduced C1q levels in severe cases [34]. These discrepancies highlight the need for further research to clarify the role of C1q in COVID-19 severity.

Interestingly, we found lower plasma C4b levels in patients who developed severe disease manifestations. This contrasts with previous reports suggesting that fragments of activated complement components would be elevated in severe patients [27–33]. Although the mechanisms underlying this finding remain speculative, it is possible that intense complement activation leads to rapid C4b deposition on viral particles and damaged tissues, thus depleting its free plasma levels. Differences in severity criteria across studies may also account for this divergence, and further investigation is warranted to confirm these hypotheses.

Beyond assessing associations between complement levels and clinical severity, we also performed a network analysis exploring the interaction between complement components and routine laboratory tests at admission. We found significant correlations between complement proteins and markers of coagulation (platelets, INR, PT and APTT) as well as kidney function (creatinine, urea).

The correlation between plasma complement activation and coagulation parameters likely reflects a complex interplay where complement activation, triggered by SARS-CoV-2, promotes endothelial injury, expression of procoagulant factors, and direct interaction with coagulation pathways [26, 45, 46]. This contributes to the hypercoagulable state and endothelial dysfunction characteristic of severe COVID-19. Similarly, complement activation can exacerbate kidney injury via local deposition of complement components, inflammation, endothelial damage, and microthrombosis [15, 37, 47], ultimately leading to impaired renal function.

Our study has several limitations. We did not assess complement activation in tissue samples, which might more accurately reflect local complement activity in response to infection. Nevertheless, the study has important strengths, including the enrollment of unvaccinated patients, a relatively large sample size, and the comprehensive analysis of complement components across all three activation pathways.

Conclusion

Our findings demonstrate, for the first time, that the complement system is associated with severe clinical outcomes in COVID-19, including the risk of ICU admission, need for invasive ventilatory support, sepsis, cardiorespiratory arrest, acute kidney failure, and death. In addition, we show that complement components correlate with laboratory parameters related to coagulation and kidney function. Together, these results enhance the understanding of how plasma complement levels are linked to clinical and laboratory markers of COVID-19 severity. Our study also suggests that complement proteins may serve as potential biomarkers of disease progression or as therapeutic targets for the treatment of COVID-19.

Supplementary Fig. 1. Heat map representing the degree of correlation between complement proteins and laboratory parameters in patients hospitalized with COVID-19. The degree of correlation was accessed using Spearman's rank correlation coefficient test. Significance was considered when $p < 0.05$. ALT: alanine transaminase; AST: aspartate transaminase; Cr: creatinine; CRP: C-reactive protein; INR: international normalized ratio; MBL: mannose-binding lectin; TBIL: total bilirubin, WBC: white blood cell.

Abbreviations

ALT	alanine aminotransferase
AP	alternative pathway
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
CAAE	certificate of submission for ethical consideration
C1q	complement protein C1q
C2	complement protein 2
C3	complement protein 3
C3b/iC3b	C3 fragments (opsonins derived from complement protein 3)
C4	complement protein 4
C5	complement protein 5
C5a	anaphylatoxin
CONEP	Brazilian National Research Ethics Commission
COVID-19	coronavirus disease 2019
COPD	chronic obstructive pulmonary disease
CP	classical pathway
CRP	C-reactive protein
EDTA	ethylenediaminetetraacetic acid
HC/UFPE	Hospital das Clínicas of the Federal University of Pernambuco
HU-UNIVASF	University Hospital of the Universidade Federal do Vale do São Francisco
INR	international normalized ratio
JASP	Jeffrey's Amazing Statistics Program
LAMUPE	Multi-User Research Laboratory
LP	lectin pathway
MAC	membrane attack complex
MBL	mannose-binding lectin
MFI	median fluorescence intensity
MASP2	MBL-associated serine protease 2
PT	prothrombin time
RT-PCR	real-time polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11663-2.

Supplementary Material 1.

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Authors' contributions

RFC conceived the study. LVA and BV obtained the data. LVA wrote the first draft of the manuscript. CDFS and LVA conducted the statistical analysis. ACA, RK, CDFS, and RFC interpreted the data. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas of the Federal University of Pernambuco (HC/UFPE) under register number CAAE: 36613520.0.0000.5640. A free and informed consent form was obtained

in accordance with the requirements of the Brazilian National Research Ethics Commission (CONEP, acronym in Portuguese).

Consent for publication
Not applicable.

Competing interests
Rodrigo Feliciano do Carmo is Senior Editor at BMC Infectious Diseases.

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