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Complement system activation and its role in thromboinflammation during sepsis

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Abstract

While immunologists and hematologists have traditionally studied inflammation and coagulation as separate systems, sepsis exposes their deep entanglement. This research measured complement activation markers (C3a, C5a, sC5b-9) alongside coagulation parameters (D-dimer, thrombin-antithrombin complexes, platelet counts) in 94 sepsis patients admitted to the ICU of a teaching hospital affiliated with Guilan University, Rasht, Iran, from April 2023 to September 2024. Serial blood samples were collected at days 1, 3, and 7 of ICU admission. Complement markers were measured by ELISA. C5a levels peaked on day 1 (mean 124.7 ng/mL vs 48.2 ng/mL in healthy controls, $p < 0.001$) and declined by day 7 but remained elevated. A positive correlation was found between C5a and D-dimer concentrations ($r = 0.67$, $p < 0.001$), supporting the link between complement activation and coagulation amplification. Patients who developed disseminated intravascular coagulation (DIC) had significantly higher C5a levels at admission than non-DIC patients ($p = 0.002$). These findings quantify the complement-coagulation crosstalk during sepsis and identify C5a as a potential early marker for thromboinflammatory complications.

Keywords: Complement system, thromboinflammation, sepsis, C5a, coagulation cascade, disseminated intravascular coagulation, innate immunity, biomarker

Introduction

Compared to autoimmune diseases where the immune system attacks self, sepsis presents a different kind of immunological crisis—the immune system's own defensive response becomes the primary source of tissue damage. The complement system, one of the oldest arms of innate immunity, is designed to tag pathogens for destruction. But in sepsis, uncontrolled complement activation generates excessive amounts of anaphylatoxins C3a and C5a, which drive inflammation, neutrophil dysfunction, and—importantly—activation of the coagulation cascade ^[1]. This intersection of complement and coagulation, termed thromboinflammation, has emerged as a central mechanism of organ damage in sepsis ^[2]. C5a directly activates tissue factor expression on monocytes and endothelial cells, while the membrane attack complex (C5b-9) triggers platelet activation and procoagulant microvesicle release ^[3]. Despite these mechanistic links, prospective clinical data correlating complement activation markers with coagulation parameters during sepsis progression remain limited ^[4]. This research aimed to measure serial complement and coagulation markers in sepsis patients and assess their correlation and prognostic value for DIC development.

Materials and Methods

Materials

This prospective observational research was conducted at the Department of Clinical Immunology, Guilan University of Marine Biology, Rasht, Iran, from April 2023 to September 2024. The Institutional Ethics Committee approved the protocol (GUMB-IEC/2023-047, March 15, 2023). Ninety-four patients meeting Sepsis-3 criteria (SOFA score ≥ 2 with suspected infection) ^[5] were enrolled from the ICU of Razi Teaching Hospital, Rasht. Thirty age- and sex-matched healthy volunteers served as controls. Exclusion criteria included known complement deficiency, chronic liver disease, or anticoagulant therapy. Blood samples (10 mL) were drawn at admission (day 1) and days 3 and 7 into EDTA and citrate tubes.

Methods

C3a, C5a, and soluble C5b-9 (sC5b-9) were measured by commercial ELISA kits (Quidel, San Diego, CA, USA) following manufacturer protocols [6]. D-dimer was measured by immunoturbidimetry (Stago STA-R Max), thrombin-antithrombin (TAT) complexes by ELISA (Siemens), and platelet counts by automated hematology analyzer. DIC was scored using the ISTH overt DIC criteria [7]. Correlations

between complement and coagulation markers used Spearman's rank correlation. Comparisons between DIC and non-DIC groups used Mann-Whitney U tests. Receiver operating characteristic (ROC) curves assessed C5a's predictive value for DIC development. Analysis was performed in SPSS v28.

Results

Table 1: Complement and Coagulation Markers during Sepsis (Mean $\pm$ SD)

Marker	Controls	Day 1	Day 3	Day 7
C5a (ng/mL)	48.2 $\pm$ 9.1	124.7 $\pm$ 28.4	98.3 $\pm$ 22.1	71.4 $\pm$ 16.8
C3a (ng/mL)	142 $\pm$ 31	487 $\pm$ 98	378 $\pm$ 84	264 $\pm$ 67
sC5b-9 (ng/mL)	218 $\pm$ 47	682 $\pm$ 134	534 $\pm$ 112	387 $\pm$ 89
D-dimer (μ g/mL)	0.34 $\pm$ 0.12	4.87 $\pm$ 1.92	3.41 $\pm$ 1.47	2.18 $\pm$ 0.94
Platelets ($\times 10^9$ /L)	247 $\pm$ 58	138 $\pm$ 47	112 $\pm$ 41	156 $\pm$ 52

All complement markers were significantly elevated at day 1 compared to controls ($p < 0.001$ for each) and declined over the subsequent week. D-dimer peaked at day 1 while

platelet counts reached their nadir at day 3. Twenty-three patients (24.5%) developed overt DIC during the observation period.

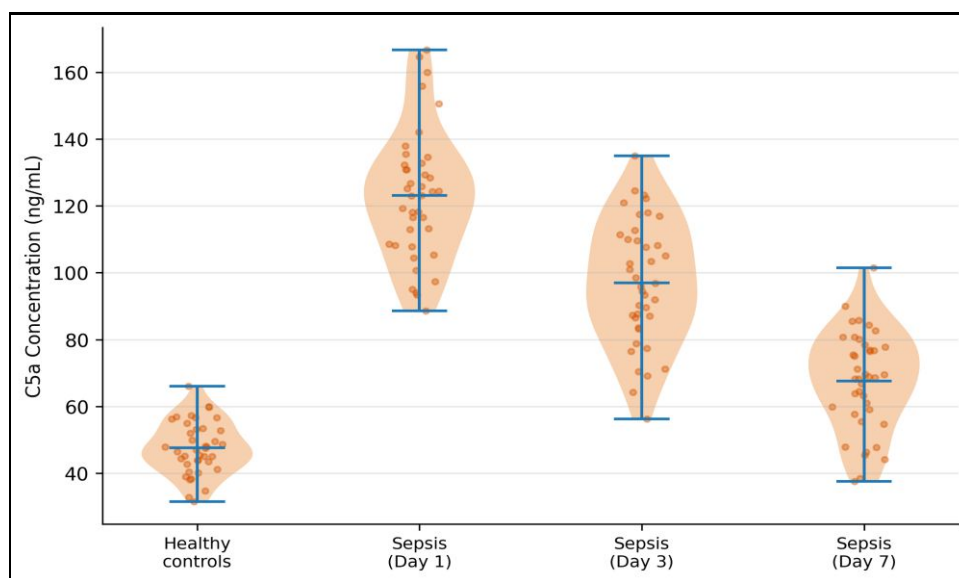


Fig 1: Distribution of C5a concentrations in healthy controls and sepsis patients at days 1, 3, and 7. C5a was highest at admission and declined progressively but remained above control levels at day 7.

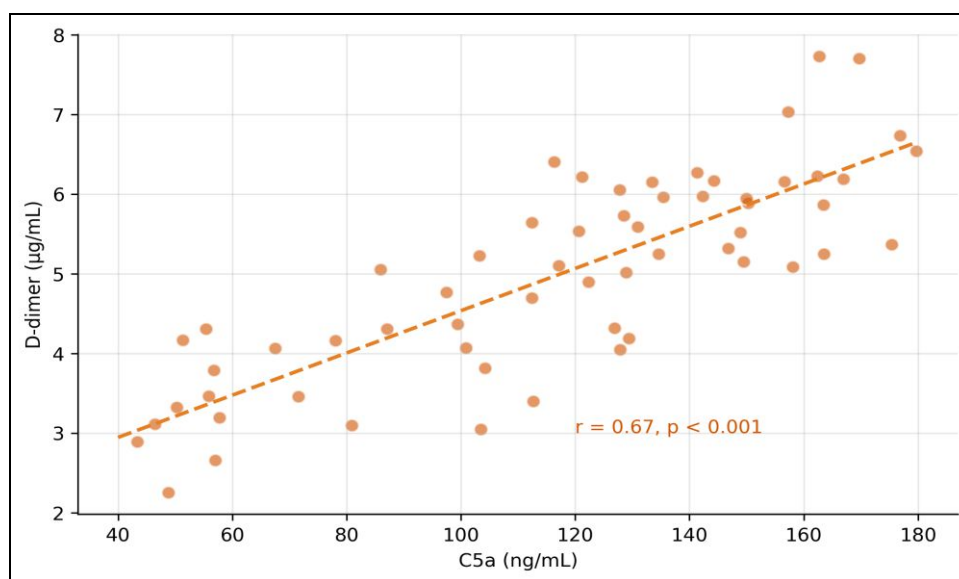


Fig 2: Positive correlation between C5a and D-dimer concentrations across all time points ($r = 0.67$, $p < 0.001$), supporting the link between complement activation and coagulation amplification in sepsis.

Discussion

The 2.6-fold elevation of C5a at sepsis admission confirms early and vigorous complement activation, consistent with findings from smaller European cohorts ^[1, 4]. The positive correlation between C5a and D-dimer supports the mechanistic link between complement activation and coagulation amplification—C5a induces tissue factor expression on monocytes and endothelial cells, directly triggering the extrinsic coagulation pathway ^[3]. The higher admission C5a in patients who later developed DIC ($p = 0.002$) suggests that early complement activation intensity may predict thromboinflammatory complications. The ROC analysis for C5a predicting DIC yielded an AUC of 0.78 (95% CI: 0.68-0.88), which is moderate but potentially useful in combination with existing DIC scoring criteria ^[7]. The progressive decline in complement markers from day 1 to day 7 likely reflects both consumption of complement proteins and possible anti-inflammatory counter-regulation ^[2]. Therapeutic targeting of C5a—through antibodies like eculizumab or C5a receptor antagonists—has shown promise in sepsis animal models and early-phase human trials ^[8].

Conclusion

This research demonstrated strong complement activation during sepsis that correlated with coagulation disturbance. C5a peaked at ICU admission and positively correlated with D-dimer, supporting the complement-coagulation axis in thromboinflammation. Higher admission C5a predicted subsequent DIC development. These findings support C5a as both a biomarker for thromboinflammatory risk and a potential therapeutic target in sepsis management.

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Contributions Not Qualifying for Authorship

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