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DYNAMIC CHANGES IN ALBUMIN AND FIBRINOGEN LEVELS DURING SEPSIS: A PROSPECTIVE OBSERVATIONAL COHORT ANALYSIS.

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Abstract

Background

Sepsis is a major cause of morbidity and mortality in critically ill patients, especially in low- and middle-income countries like India. Albumin and fibrinogen are key plasma proteins with opposing kinetic responses during inflammation and may serve as useful biomarkers in sepsis. This study aims to evaluate the kinetics of albumin and fibrinogen in septic patients to better understand their correlation with disease severity and outcomes.

Methods

This prospective, observational, comparative study was conducted at RIMS, Ranchi, over 12 months. Fifty-five patients (37 septic, 18 non-septic) were enrolled. Hepatic protein synthesis was assessed using stable isotope-labeled L-[ring-$^2H_5$] phenylalanine infusion, followed by GC-MS analysis to determine FSR and ASR of albumin and fibrinogen.

Results

Septic patients had significantly lower plasma albumin and higher fibrinogen levels ($p < 0.001$). Albumin FSR was elevated ($p = 0.03$) without a significant change in ASR ($p = 0.42$), while both FSR and ASR of fibrinogen were significantly increased ($p = 0.01$, <0.001). The albumin/fibrinogen ASR ratio was markedly reduced ($p < 0.001$), indicating a shift toward acute-phase protein production in sepsis.

Conclusion

Sepsis is associated with hypoalbuminemia despite increased synthesis, likely due to elevated clearance. Hepatic protein synthesis shifts toward fibrinogen, reflecting a prioritized acute-phase response.

Recommendation

Future research with larger, multi-center cohorts is recommended to validate these findings and further investigate the biochemical differences between septic and non-septic patients. Exploring hepatic protein synthesis parameters may also offer valuable insights for clinical applications in sepsis management.

Keywords: *Sepsis, albumin, fibrinogen, hepatic protein synthesis, stable isotope tracer, acute-phase response.*
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Introduction

Sepsis is a severe and life-threatening condition characterized by organ dysfunction resulting from a dysregulated immune response to infection. It continues to pose a major health burden worldwide, with the highest impact observed in developing countries. In 2017, India alone accounted for approximately 11.3 million sepsis cases—around 23.1% of the global burden—and 2.9 million deaths, reflecting a mortality rate of nearly 297.7 per 100,000 population. The prevalence of sepsis in Indian ICUs has been reported to range between 33.2% and 56.4%, with 30-day mortality rates reaching up to 27.6%. Gram-negative bacterial infections are the most common cause, often complicated by multidrug resistance, making early diagnosis and appropriate monitoring essential for improving outcomes in critically ill patients [1,2].

Albumin and fibrinogen are two key plasma proteins whose kinetics are significantly altered during sepsis.

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Albumin, the most abundant protein in plasma, has a half-life of 17–19 days and is predominantly synthesized by the liver. It plays an essential role in maintaining colloidal osmotic pressure, transporting various substances, and regulating acid-base balance. In sepsis, hypoalbuminemia is a common finding and may result from reduced hepatic synthesis, increased vascular leakage, or enhanced degradation. In contrast, fibrinogen is a positive acute-phase reactant that increases in response to systemic inflammation, contributing to the prothrombotic state in septic patients. While hypoalbuminemia is often associated with poor prognosis, elevated fibrinogen levels can indicate an ongoing inflammatory response, making both proteins important markers in sepsis pathophysiology [3,4,5,6].

Understanding the relationship between albumin and fibrinogen kinetics in the context of sepsis is crucial for both prognostication and therapeutic guidance. However, limited studies have evaluated their concurrent behavior in septic patients over time. This prospective observational study assessed the dynamic changes of serum albumin and fibrinogen levels in sepsis and explored how their patterns correlate with disease progression and clinical outcomes. This study aims to evaluate the kinetics of albumin and fibrinogen in septic patients to better understand their correlation with disease severity and outcomes. The justification for this work lies in the potential of these biomarkers to serve as accessible, cost-effective tools for monitoring sepsis severity and guiding timely interventions in resource-constrained settings.

Methods

Study Design

This study was conducted as a prospective, observational, comparative cohort study at the Rajendra Institute of Medical Sciences (RIMS), Ranchi.

Study Duration and Setting

The study was conducted at the Rajendra Institute of Medical Sciences (RIMS), Ranchi, over 12 months (from January 2023 to December 2023). Participants were enrolled from the ICU for septic patients and from the surgical wards for non-septic patients.

Sample Size

The study encompassed 55 participants who were divided into two cohorts: Group S (septic patients) and Group NS (non-septic patients), with group allocation based on clinical criteria.

Inclusion Criteria

- Patients aged 18–75 years
- Sepsis group: Diagnosed with sepsis according to Sepsis-3 criteria (SOFA score ≥2 due to infection)
- Control group: Patients undergoing elective abdominal surgery under general anesthesia
- Hemodynamically stable at the time of inclusion
- Provided informed consent or had a legal representative provide consent

Exclusion Criteria

- Moribund patients or those expected to die within 48 hours
- Patients requiring extracorporeal support (e.g., dialysis, ECMO)
- Known chronic liver disease or decompensated liver function
- Active malignancy
- BMI <18.5 or >35 kg/m²
- Recent (within 4 weeks) blood transfusion
- Pregnant or lactating women

Ethical Considerations

Prior approval for the study was obtained from the Institutional Ethics Committee of RIMS, Ranchi. All participants or their legally authorized representatives provided informed written consent.

Data Collection

Demographic data, clinical history, and vital parameters were recorded at baseline. For septic patients, severity scoring systems such as the APACHE II and SOFA scores were documented at the time of inclusion. In the control group, clinical evaluation was performed one day before elective surgery. Laboratory parameters including complete blood count, liver function tests, renal function tests, and inflammatory markers (CRP, procalcitonin) were also noted. Details regarding the source of infection, antibiotic therapy, and organ dysfunction were collected for patients in the sepsis group.

Assessment of Protein Levels

The study protocol for assessing albumin and fibrinogen kinetics in sepsis was adapted from the methodology employed by Castillo et al. (1994), who investigated phenylalanine and tyrosine kinetics in critically ill pediatric patients with sepsis [7]. The present study utilized a similar primed-constant infusion technique using L-[ring-$^{2}H_{5}$]phenylalanine to specifically assess the synthesis kinetics of hepatic-derived proteins—albumin and fibrinogen. Following a 12-hour fasting period, patients received a priming dose of 4 µmol/kg, followed by a continuous infusion at 0.15 µmol/kg/min over six hours. Hourly blood samples were collected from 8 AM

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to 2 PM. Plasma was immediately separated and treated with protease inhibitors to prevent degradation. Fibrinogen was precipitated from plasma using an ethanol-saline solution, while albumin was extracted from the supernatant. Both proteins underwent purification through SDS-PAGE, followed by hydrolysis and tracer enrichment analysis via gas chromatography-mass spectrometry (GC-MS). The precursor pool enrichment was estimated using very low-density lipoprotein (VLDL) apolipoprotein B-100. The fractional synthesis rate (FSR) and absolute synthesis rate (ASR) of albumin and fibrinogen were then calculated using established kinetic models, incorporating patient-specific plasma volumes and protein concentrations. This adapted protocol enabled precise, dynamic quantification of hepatic protein synthesis in sepsis, offering insights into altered metabolic responses during systemic inflammation.

Statistical Analysis

Data were analyzed using SPSS v20.0. Appropriate parametric or non-parametric tests, such as the chi-square test were applied, with $p < 0.05$ considered statistically significant.

Results

The study included 55 participants, with 18 in the non-septic group and 37 in the septic group. While the septic group was slightly older (mean age 65.1 ± 9.4 years vs. 60.7 ± 10.3 years), the difference was not statistically significant ($p = 0.18$). There were more males in both groups, but gender distribution did not differ significantly ($p = 0.21$). Body Mass Index (BMI) and prevalence of Type 2 Diabetes Mellitus (T2DM) were comparable between groups. However, vasopressor use was significantly more frequent in the septic group (45.4% vs. 5.5%, $p < 0.001$), reflecting greater hemodynamic instability (Table 1).

Table 1: Demographic, Clinical, and Biochemical Characteristics of Study Participants

Parameter	Non-Septic Group (n = 18)	Septic Group (n = 37)	*P* value
Mean Age (years)	60.7 ± 10.3	65.1 ± 9.4	0.18
Male – n (%)	13 (72%)	20 (54%)	0.21
BMI (kg/m²)	26.5 ± 4.2	27.8 ± 5.1	0.39
T2DM – n (%)	3 (17%)	11 (30%)	0.33
Vasopressor Use – n (%)	1 (5.5%)	17 (45.4%)	<0.001

The severity of illness, as assessed by APACHE II and SOFA scores, was significantly higher in Group S ($p = 0.02$ and $p = 0.001$, respectively). Hematological parameters showed lower hemoglobin and platelet counts in group S ($p = 0.01$ and $p = 0.03$), alongside markedly elevated total leukocyte counts ($p < 0.001$). Renal function markers were impaired in sepsis, with significantly elevated serum creatinine and blood urea nitrogen ($p = 0.005$ and $p < 0.001$). Inflammatory markers, including CRP and procalcitonin, were substantially elevated in group S ($p < 0.001$), supporting the presence of systemic inflammation and infection (Table 2).

Table 2: Clinical Parameters in Non-Septic and Septic Patients

Parameter	Non-Septic Group (n = 18)	Septic Group (n = 37)	P-value
Severity Scoring Systems			
APACHE II Score (median, IQR)	11.0 (9.0–14.0)	15.0 (12.0–18.0)	0.02
SOFA Score (median, IQR)	3.0 (2.0–4.0)	6.0 (4.0–8.0)	0.001
Complete Blood Count			
Hemoglobin (g/dL)	12.7 ± 1.0	11.4 ± 1.3	0.01
Total Leukocyte Count (×10⁹/L)	8.9 ± 2.4	14.8 ± 5.1	<0.001
Platelet Count (×10⁹/L)	215 ± 58	172 ± 50	0.03
Renal Function Tests			
Serum Creatinine (mg/dL)	0.96 ± 0.22	1.38 ± 0.54	0.005
Blood Urea Nitrogen (mg/dL)	23.4 ± 6.7	40.1 ± 13.6	<0.001
Inflammatory Markers			
C-Reactive Protein (CRP) (mg/L)	26.7 ± 10.9	98.6 ± 36.4	<0.001
Procalcitonin (ng/mL)	0.10 ± 0.07	5.4 ± 2.9	<0.001

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The results in Table 3 highlight significant differences in hepatic protein synthesis parameters between the 2 cohorts. Patients belonging to cohort S exhibited markedly lower albumin concentrations (27.1 ± 4.2 g/L) compared to group NS (42.7 ± 3.8 g/L), while fibrinogen concentrations were significantly elevated in the septic group (5.3 ± 1.9 g/L vs. 1.8 ± 0.6 g/L; $p < 0.001$). Both albumin and fibrinogen fractional synthesis rates (FSR) were higher in septic patients, indicating an upregulated acute-phase protein response. Despite the elevated albumin FSR in sepsis, the albumin absolute synthesis rate (ASR) was lower (225.3 ± 98.1 mg/kg/day) compared to the non-septic group (274.2 ± 84.7 mg/kg/day), though not statistically significant. In contrast, fibrinogen ASR was significantly higher in septic patients (102.5 ± 55.4 mg/kg/day vs. 27.9 ± 13.6 mg/kg/day; $p < 0.001$). The albumin-to-fibrinogen ASR ratio was substantially reduced in the septic group (2.9 ± 3.6), underscoring a metabolic shift favoring fibrinogen production during sepsis.

Table 3: Hepatic Protein Synthesis Parameters among the 2 groups

Parameter	Non-Septic Group (n = 18)	Septic Group (n = 37)	P value
Albumin Concentration (g/L)	42.7 ± 3.8	27.1 ± 4.2	< 0.001
Fibrinogen Concentration (g/L)	1.8 ± 0.6	5.3 ± 1.9	< 0.001
Albumin FSR (%/day)	14.3 ± 5.2	20.5 ± 7.1	0.02
Fibrinogen FSR (%/day)	29.6 ± 10.4	47.9 ± 15.8	0.008
Albumin ASR (mg/kg/day)	274.2 ± 84.7	225.3 ± 98.1	0.39
Fibrinogen ASR (mg/kg/day)	27.9 ± 13.6	102.5 ± 55.4	< 0.001
Albumin/Fibrinogen ASR Ratio	13.7 ± 6.1	2.9 ± 3.6	< 0.001

Discussion

This study demonstrated that septic patients had significantly lower plasma albumin levels compared to non-septic controls, despite a higher FSR and comparable ASR of albumin. In contrast, both FSR and ASR of fibrinogen were significantly elevated in the septic group, accompanied by higher plasma fibrinogen levels. The albumin-to-fibrinogen ASR ratio was markedly reduced in sepsis, indicating a preferential hepatic shift toward acute-phase protein production. These findings are consistent with previous studies showing that hypoalbuminemia in sepsis results from increased clearance rather than decreased synthesis, while elevated fibrinogen levels reflect enhanced hepatic production as part of the acute-phase response [8].

The observed dissociation between plasma albumin levels and hepatic synthesis rates in septic patients highlights the complexity of albumin metabolism during systemic inflammation. Although albumin FSR was elevated, likely reflecting a hepatic compensatory response, the unchanged ASR suggests that increased synthesis was insufficient to offset accelerated clearance, redistribution, or catabolism associated with sepsis [9,10]. These findings challenge the assumption that hypoalbuminemia in sepsis is solely a result of suppressed hepatic production and instead support the hypothesis of increased peripheral loss [11,12].

Conversely, the significant increase in both FSR and ASR of fibrinogen in septic patients emphasizes the liver's acute-phase response, likely driven by inflammatory mediators such as IL-6 [13]. Elevated fibrinogen levels are consistent with the pro-coagulant and immune-modulatory roles of this protein in sepsis and reflect a strategic hepatic shift toward proteins essential for host defense and tissue repair.

The marked reduction in the albumin-to-fibrinogen ASR ratio reinforces this metabolic reprioritization. Clinically, this shift may contribute to the pro-thrombotic state observed in sepsis and serve as a potential biomarker of disease severity [14,15]. These findings also raise therapeutic considerations, such as the relevance of albumin supplementation and the potential benefits of targeting hepatic metabolic pathways to restore synthetic balance.

While the use of stable isotope tracers provides robust insights into in vivo protein kinetics, the study's limitations include its small sample size and potential variability in patient nutritional status and inflammatory burden. Further, longitudinal studies are required to assess if dynamic monitoring of hepatic protein synthesis could guide individualized interventions in septic patients.

Conclusion

This study demonstrates that sepsis significantly alters hepatic protein synthesis dynamics, characterized by a marked increase in both fractional and absolute synthesis rates of fibrinogen and a relative suppression of albumin production, despite an elevated fractional synthesis rate of albumin. This suggests a preferential hepatic shift toward acute-phase protein production in response to systemic inflammation. The resulting hypoalbuminemia and hyperfibrinogenemia reflect an adaptive but potentially maladaptive metabolic response to sepsis. The reduced albumin-to-fibrinogen ASR ratio further underscores the

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imbalance in protein synthesis. These findings reinforce the concept of hepatic reprioritization during sepsis and align with previous research on inflammatory metabolic reprogramming. Such alterations may serve as valuable biomarkers for assessing sepsis severity and monitoring therapeutic interventions.

Generalizability

The findings of this study are specific to septic and non-septic patients in a single tertiary care hospital (RIMS, Ranchi) and may not be directly generalizable to other populations with different demographic characteristics, healthcare settings, or geographic locations. However, the study provides valuable insights into the clinical and biochemical differences between septic and non-septic patients, which could inform similar studies in other settings.

Limitations

The study is limited by its single-center design, relatively small sample size, and the exclusion of certain high-risk patients (e.g., moribund patients, those with chronic liver disease or active malignancy). The findings may not be fully representative of patients in other regions or with different comorbidities. Additionally, the observational design limits causal inferences.

List of Abbreviations

- ICU: Intensive Care Unit
- RIMS: Rajendra Institute of Medical Sciences
- SOFA: Sequential Organ Failure Assessment
- ECMO: Extracorporeal Membrane Oxygenation
- BMI: Body Mass Index
- REC: Research Ethics Committee

Study Funding

The study did not receive any external funding or grants. It was self-funded by the institution (RIMS, Ranchi).

Conflict of Interest

The authors declare no conflicts of interest in the conduct or publication of this study.

Data Availability

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Author Contribution

All authors contributed equally to the design, data collection, analysis, and manuscript preparation.

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