RESEARCH PAPER

Neurovascular Balance in Septic Wistar Rats: Evaluating the GFAP/Syndecan-1 Ratio Following High and Low Volume Normal Saline versus Albumin Resuscitation

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ABSTRACT

Background: Astrocytic reactivity and endothelial glycocalyx injury are interrelated components of sepsis-associated encephalopathy (SAE). Glial fibrillary acidic protein (GFAP) reflects astrocytic activation, whereas syndecan-1 (Sdc1) is linked to endothelial glycocalyx biology. We explored whether the GFAP/Sdc1 mRNA expression ratio could serve as an integrated index of the neurovascular response to different fluid-resuscitation strategies.

Methods: Twenty adult male Wistar rats underwent cecal ligation and puncture and were randomly allocated to four groups (n = 5 per group): no fluid resuscitation, high-volume 0.9% saline (30 mL/kg), low-volume 0.9% saline (10 mL/kg), or 5% albumin (10 mL/kg). Fluids were administered intravenously 21 hours after sepsis induction. Twenty-four hours later, cortical GFAP and Sdc1 mRNA expression was quantified by one-step reverse-transcription quantitative polymerase chain reaction and normalized to GAPDH.

Results: GFAP expression was highest after 5% albumin (3.55-fold versus the unresuscitated septic control; $p < 0.05$), followed by low-volume saline (2.90-fold; $p < 0.10$) and high-volume saline (2.66-fold; $p > 0.10$). Sdc1 expression was approximately 20% lower with albumin and 25% lower with low-volume saline than in the unresuscitated septic control, whereas high-volume saline increased Sdc1 expression; these Sdc1 differences were not statistically significant. The derived GFAP/Sdc1 ratio was highest with albumin, intermediate with low-volume saline, and lowest with high-volume saline.

Conclusions: In this exploratory rat model, low-volume 5% albumin produced the most favorable GFAP/Sdc1 expression profile, whereas high-volume saline produced the least favorable profile. Because Sdc1 mRNA is not a direct measure of glycocalyx shedding and the ratio has not been clinically validated, these findings should be considered hypothesis-generating and require confirmation using protein, structural, functional, and human outcome measures.

Keywords: *sepsis-associated encephalopathy; astrocyte reactivity; endothelial glycocalyx; glial fibrillary acidic protein; syndecan-1; fluid resuscitation; blood-brain barrier*
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INTRODUCTION

Sepsis is a life-threatening syndrome of organ dysfunction caused by a dysregulated host response to infection and remains associated with substantial mortality and long-term morbidity worldwide.[1, 2] Neurological involvement is common and may manifest as sepsis-associated encephalopathy (SAE), an acute diffuse brain dysfunction characterized by delirium, altered consciousness, or coma, with some survivors experiencing persistent cognitive and neurological impairment.[3]

The pathobiology of SAE involves interacting inflammatory, glial, microvascular, and blood-brain barrier (BBB) abnormalities. Systemic inflammation can injure the cerebral endothelium, increase vascular permeability, and facilitate the entry of circulating mediators into the central nervous system. Astrocytes simultaneously undergo reactive changes that may support BBB repair and neuronal homeostasis but can also contribute to neuroinflammation depending on their phenotype, magnitude, and timing.[3-5]

GFAP is an intermediate filament protein that is commonly used as a marker of astrocytic reactivity. Increased GFAP expression after septic injury therefore indicates astroglial activation, although it does not by itself establish whether the response is protective or harmful.[4, 5] The endothelial glycocalyx is a proteoglycan-rich luminal layer that regulates vascular permeability, leukocyte-endothelial interactions, and microcirculatory homeostasis. Syndecan-1 is a major glycocalyx component, and elevated circulating Sdc1 is widely used as a marker of glycocalyx shedding and endothelial injury in sepsis.[6-11]

GFAP and Sdc1 may therefore represent complementary aspects of neurovascular stress: astrocytic activation and endothelial glycocalyx disturbance. We hypothesized that a derived GFAP/Sdc1 mRNA expression ratio could provide an exploratory summary of these concurrent responses. However, brain-tissue Sdc1 transcription should not be interpreted as a direct measurement of circulating glycocalyx shedding; increased or decreased tissue expression may reflect injury, cellular turnover, or compensatory synthesis. Accordingly, the ratio evaluated in this study is a hypothesis-generating molecular index rather than a validated biomarker.

Fluid type and dose may influence the neurovascular unit during sepsis. Large-volume saline can contribute to hyperchloremic acidosis, interstitial edema, endothelial dysfunction, and glycocalyx injury, whereas albumin has oncotic, ligand-binding, antioxidant, and anti-inflammatory properties that may support microvascular integrity.[9, 11-17] Nevertheless, clinical evidence remains mixed: albumin may improve selected hemodynamic variables or reduce net fluid balance, but a consistent survival advantage over crystalloids has not been demonstrated.[18, 19]

We therefore evaluated the effects of four resuscitation strategies—no fluid, high-volume 0.9% saline, low-volume 0.9% saline, and low-volume 5% albumin—on cortical GFAP and Sdc1 mRNA expression in a rat model of polymicrobial sepsis induced by cecal ligation and puncture (CLP). We hypothesized that low-volume albumin would produce a more favorable balance of astrocytic and endothelial responses than high-volume saline.

MATERIALS AND METHODS

Study design, animals, and ethical approval

This exploratory, controlled animal experiment used adult male Wistar rats weighing 250-300 g. Animals were obtained from a laboratory animal center and acclimatized for at least one week under standard conditions, including a 12-hour light-dark cycle and ad libitum access to food and water. All procedures were approved by the Research Ethics Committee of Universitas Padjadjaran, Bandung (Approval No. 5/UN6.KEP/EC/2025) and were conducted in accordance with applicable National Institutes of Health guidance for the care and use of laboratory animals.

Sample size and experimental allocation

The experiment was designed as an exploratory proof-of-concept study with equal allocation of five animals to each of four groups (total n = 20). This group size was selected to identify large biological signals while limiting animal use in accordance with the reduction principle. The study was intended to generate preliminary effect and variance estimates for future adequately powered experiments and was not designed to provide definitive estimates of small or moderate treatment effects. Animals were randomly assigned to the experimental groups.

Sepsis induction

Polymicrobial sepsis was induced using CLP. Rats were anesthetized with ketamine and xylazine, and a 2-3 cm midline laparotomy was performed under sterile conditions. The cecum was ligated below the ileocecal valve at approximately 50% of its length and punctured twice using a sterile 21-gauge needle. A small amount of fecal material was gently expressed, after which the cecum was returned to the abdominal cavity and the incision was closed. This procedure was used to model intra-abdominal polymicrobial sepsis. Septic animals that received no resuscitation served as the control group.

Fluid-resuscitation protocol

At 21 hours after CLP, animals received one of the following interventions:

1. Septic control: no resuscitation fluid after CLP.

2. High-volume saline: 0.9% saline, 30 mL/kg body weight, administered intravenously through the tail vein as a bolus.

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3. Low-volume saline: 0.9% saline, 10 mL/kg body weight, administered intravenously through the tail vein as a bolus.

4. Low-volume albumin: 5% human albumin, 10 mL/kg body weight (Octaserum 5%, Octapharma/Kalbe Farma), administered intravenously through the tail vein as a bolus.

No antibiotics or vasopressors were administered during the experimental period to isolate the molecular effects of fluid type and volume. Animals were monitored for pain and distress, and additional analgesia was administered when required.

Tissue collection

Twenty-four hours after fluid administration, rats were anesthetized with ketamine and xylazine and euthanized. Death was confirmed by cessation of cardiac and respiratory activity. The brain was removed promptly, and cerebral cortical tissue was dissected for molecular analysis. Samples were preserved in RNAlater and stored at -20 °C until processing. Perfusion fixation was not performed because histological analysis was outside the scope of this experiment.

RNA extraction and quantitative reverse-transcription PCR

Total RNA was extracted from RNAlater-preserved cortical tissue using the Quick-RNA Miniprep Plus Kit (Zymo Research) according to the manufacturer's protocol. Samples were homogenized in DNA/RNA Shield Buffer, treated with Proteinase K, centrifuged, lysed, filtered, precipitated with ethanol, and treated with DNase I to minimize genomic DNA contamination. Purified RNA was eluted in DNase/RNase-free water and stored at -20 °C until analysis.

One-step reverse-transcription quantitative PCR was performed using SensiFAST SYBR No-ROX One-Step Mix (Bioline). Primer sequences were as follows: GFAP forward 5′-CGAGATCGCCACCTACAGGA-3′ and reverse 5′-TCGACTCCTTAATGACCTCGCC-3′; Sdc1 forward 5′-CGGCAACTCCGACCCACATA-3′ and reverse 5′-GGAGGCACATTTGCGGTGAC-3′. GAPDH served as the housekeeping gene. Relative expression was calculated using the 2^-Ct method and normalized to the unresuscitated septic control. A derived GFAP/Sdc1 expression ratio was calculated from the normalized relative expression values.

Statistical analysis

Data distributions were assessed before inferential analysis. Descriptive statistics were calculated, and groups were compared using one-way analysis of variance. When the omnibus test was significant, Tukey's post hoc test was used for pairwise comparisons. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Results with $0.05 \leq p < 0.10$ were described as nonsignificant trends rather than statistically significant findings. Given the small sample size, all inferential results were interpreted as exploratory.

RESULTS

GFAP mRNA expression

Cortical GFAP mRNA expression varied across resuscitation strategies. The 5% albumin group showed the largest increase, with expression 3.55-fold higher than the unresuscitated septic control ($p < 0.05$). Low-volume saline produced a 2.90-fold increase ($p < 0.10$), representing a nonsignificant trend. High-volume saline produced a 2.66-fold increase that was not statistically significant ($p > 0.10$). These findings indicate the strongest astrocytic transcriptional response in the albumin group, although the small sample size limits the precision of between-group estimates.

Sdc1 mRNA expression

Sdc1 mRNA expression showed a different, but statistically nonsignificant, pattern. Compared with the unresuscitated septic control, Sdc1 expression was approximately 20% lower in the albumin group and 25% lower in the low-volume saline group (both $p > 0.10$). In contrast, high-volume saline increased Sdc1 expression relative to the other groups. Because the differences were not statistically significant and tissue Sdc1 transcription is not a direct assay of glycocalyx shedding, these findings should be interpreted as preliminary evidence of differential endothelial molecular responses rather than proof of glycocalyx preservation or degradation.

GFAP/Sdc1 Expression Ratio

The derived GFAP/Sdc1 ratio was used to summarize the relative balance between astrocytic and endothelial molecular responses. The ratio was highest in the 5% albumin group, in which increased GFAP expression occurred alongside lower Sdc1 expression. Low-volume saline produced an intermediate ratio, whereas high-volume saline produced the lowest ratio because its relatively modest GFAP increase occurred together with increased Sdc1 expression.

Overall, the expression pattern suggested that fluid type and volume influenced the neurovascular molecular response to sepsis. Albumin produced the most favorable exploratory ratio, low-volume saline produced an intermediate profile, and high-volume saline produced the least favorable profile. These group-level patterns require confirmation in larger experiments with direct protein, histological, physiological, and neurological outcomes.

DISCUSSION

This exploratory study found that resuscitation fluid type and volume were associated with different cortical GFAP and Sdc1 mRNA expression patterns after CLP-induced sepsis. Low-volume 5% albumin produced the highest GFAP/Sdc1 ratio, low-volume saline produced an intermediate ratio, and high-volume saline produced the lowest ratio. The results are consistent with the hypothesis that albumin may support a more favorable neurovascular molecular environment than aggressive saline loading;

however, the ratio is unvalidated and the study did not directly measure glycocalyx shedding, BBB permeability, neurological function, or survival.

Interpretation of the albumin-associated profile

The albumin group showed the strongest GFAP transcriptional response together with lower Sdc1 expression. Albumin may support the microcirculation through oncotic effects, ligand transport, antioxidant activity, and interactions with the endothelial surface layer.[16, 17] Nevertheless, increased GFAP should not automatically be interpreted as neuroprotection, and lower tissue Sdc1 expression should not be equated with reduced circulating glycocalyx shedding. The present findings therefore support a mechanistic hypothesis rather than a definitive protective effect.

Recent clinical evidence also requires a cautious interpretation. In ALBIOS, albumin supplementation was associated with a higher mean arterial pressure and lower net fluid balance but did not improve 28- or 90-day survival.[19] The 2024 ABC-Sepsis feasibility trial successfully compared 5% albumin with balanced crystalloid during early emergency-department resuscitation, but it was not powered to establish efficacy and its point estimates did not demonstrate albumin superiority.[20] A 2025 randomized trial of 20% albumin in fluid-responsive septic patients reported short-term improvements in sublingual microcirculatory measures without differences in mortality, vasopressor duration, fluid balance, or intensive-care length of stay.[21] The 2026 ARISS trial similarly found that albumin was safe but did not significantly improve 90-day survival, although premature termination limited statistical power.[22] These human studies suggest that albumin may affect hemodynamic or microcirculatory endpoints without establishing a routine survival benefit.

Interpretation of the high-volume saline profile

High-volume saline produced the lowest GFAP/Sdc1 ratio, reflecting a relatively modest GFAP response combined with increased Sdc1 expression. Potential mechanisms include hemodilution, increased hydrostatic pressure, interstitial edema, and a high chloride load that may promote hyperchloremic acidosis and endothelial stress.[9, 11-15] However, no serum chloride, acid-base, cerebral edema, or BBB permeability measurements were obtained; these explanations therefore remain biologically plausible but unconfirmed in this experiment.

The findings should also not be generalized to all crystalloids. The experimental comparator was 0.9% saline, whereas contemporary human resuscitation frequently uses balanced crystalloid solutions. Future studies should therefore distinguish the effects of saline volume from those of crystalloid composition and should use fluid-responsiveness criteria rather than fixed-volume administration alone.

Interpretation of the low-volume saline profile

Low-volume saline produced an intermediate GFAP/Sdc1 ratio. The 2.90-fold GFAP increase represented a nonsignificant trend, while Sdc1 expression was modestly lower than in the unresuscitated septic control. This pattern may reflect partial restoration of perfusion without the fluid and chloride burden associated with the high-volume saline regimen. Because the relevant comparisons were imprecise and Sdc1 changes were not statistically significant, the result should be interpreted as preliminary rather than evidence of a protective effect.

Translational implications and future human studies

The principal translational value of this experiment is the identification of a testable neurovascular framework rather than support for immediate changes in clinical practice. A human study should prospectively compare protocolized, fluid-responsive resuscitation strategies and include balanced crystalloids, saline, and albumin where clinically appropriate. Serial plasma GFAP and Sdc1 measurements should be paired with established endothelial and BBB markers, hemodynamic and microcirculatory assessments, delirium screening, neurocognitive outcomes, organ-support requirements, fluid balance, and mortality. Repeated sampling would help determine whether the ratio has temporal, prognostic, or treatment-response value.

Before clinical testing, the ratio should be validated in larger animal studies using individual-level data, prespecified calculation methods, protein quantification, immunohistochemistry, circulating Sdc1, BBB permeability assays, cerebral edema measurements, and behavioral outcomes. Dose-response studies should compare albumin concentrations and balanced crystalloids, incorporate antibiotics and vasopressors, and evaluate both sexes. These steps are necessary to determine whether the observed transcriptional pattern represents neurovascular protection, compensatory expression, or an epiphenomenon.

Limitations

This study has several limitations. First, the sample size was small (n = 5 per group), limiting precision and the ability to detect small or moderate effects. Second, no sham-operated nonseptic group was included; all comparisons were therefore relative to unresuscitated sepsis rather than healthy baseline conditions. Third, only adult male rats were studied, and the CLP model represents abdominal polymicrobial sepsis but does not reproduce the heterogeneity, comorbidity burden, age distribution, or supportive care of human sepsis. Antibiotics and vasopressors were intentionally withheld, and a fixed bolus administered 21 hours after CLP differs from titrated clinical resuscitation. The use of human albumin in rats may also introduce species-specific biological effects.

Fourth, measurements were limited to cortical mRNA at a single time point. Transcript abundance may not correspond to protein concentration, cellular localization, circulating shedding, or functional BBB integrity. Sdc1 mRNA is therefore an indirect and potentially compensatory marker rather than a direct assay of glycocalyx degradation. Fifth, the GFAP/Sdc1 ratio has

not been externally validated, and the study did not assess plasma biomarkers, histology, BBB permeability, cerebral edema, regional brain differences beyond the sampled cortex, neurological behavior, cognition, or survival. These limitations preclude causal or clinical conclusions and emphasize the exploratory nature of the findings.

CONCLUSION

In this exploratory CLP model, low-volume 5% albumin produced the highest cortical GFAP/Sdc1 mRNA expression ratio, low-volume saline produced an intermediate ratio, and high-volume saline produced the lowest ratio. The findings identify a potential relationship between resuscitation strategy and the balance of astrocytic and endothelial molecular responses. They do not establish that albumin prevents glycocalyx injury or improves neurological outcomes, and they do not support routine albumin use in human sepsis. Validation with direct structural and functional measures, larger animal cohorts, and carefully designed human studies is required.

Abbreviations

ANOVA	Analysis of variance
BBB	Blood-brain barrier
CLP	Cecal ligation and puncture
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GFAP	Glial fibrillary acidic protein
mRNA	Messenger ribonucleic acid
NVU	Neurovascular unit
RNA	Ribonucleic acid
RT-qPCR	Reverse-transcription quantitative polymerase chain reaction
SAE	Sepsis-associated encephalopathy
Sdc1	Syndecan-1

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Author contributions

PRH, TTM, AMM, EJW, NS, TMR, and S designed the study. PRH and NS established the animal model and performed the animal experiments. PRH, TTM, and AMM analyzed and interpreted the data and drafted the manuscript. TTM and AMM provided critical intellectual revisions. All authors read and approved the final manuscript.

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Availability of data and materials

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

DECLARATIONS

Ethics Approval and Consent To Participate

All procedures were approved by the Research Ethics Committee of Universitas Padjadjaran, Bandung (Approval No. 5/UN6.KEP/EC/2025) and were conducted in accordance with applicable National Institutes of Health guidance for the care and use of laboratory animals.

Consent for Publication

All authors approved submission of the manuscript for publication.

Competing Interests

The authors declare that they have no competing interests.

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