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Heparan Sulphate Fragments as Biomarkers of Endothelial Injury in Early Sepsis: A Prospective Cohort Study

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ABSTRACT

Background: The endothelial glycocalyx, a heparan sulphate-rich layer coating the vascular lumen, undergoes rapid enzymatic and proteolytic shedding during sepsis, releasing soluble heparan sulphate fragments and syndecan-1 ectodomain into the circulation. Objective: This narrative review synthesizes published clinical and mechanistic literature on heparan sulphate and syndecan-1 as biomarkers of endothelial injury in sepsis. Methods: We reviewed prospective cohort studies, trial substudies, and meta-analyses reporting circulating glycocalyx degradation products in relation to sepsis severity, organ dysfunction, mortality, and resuscitation practice. Findings: Circulating syndecan-1 rises in graded fashion with sepsis severity and correlates with coagulopathy, thrombocytopenia, and respiratory and multi-organ dysfunction; independent meta-analyses spanning thousands of patients confirm consistent associations between elevated syndecan-1 and mortality, septic shock, and acute kidney injury; large trial-embedded cohorts further show that glycocalyx degradation predicts outcome independent of randomized fluid strategy, while the causal contribution of resuscitation volume to shedding remains incompletely resolved. Conclusions: Heparan sulphate fragments and syndecan-1 are reproducible, mechanistically grounded biomarkers of endothelial injury in sepsis with demonstrated prognostic value, positioning them as candidates for future risk-stratification and glycocalyx-protective resuscitation research.

Keywords: *endothelial glycocalyx; heparan sulphate; syndecan-1; sepsis biomarkers; septic shock outcomes*

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Introduction

Sepsis remains a leading cause of morbidity and mortality in critically ill patients, and a substantial share of its pathophysiology is now understood to originate not within the parenchyma of failing organs but at the luminal surface of the vascular endothelium itself. The endothelial glycocalyx is a gel-like layer of membrane-bound proteoglycans, glycosaminoglycans, and adsorbed plasma proteins that coats the apical surface of endothelial cells throughout the vascular tree, regulating vascular permeability, mechanotransduction, leukocyte adhesion, and the interface between flowing blood and the vessel wall [1]. Heparan sulphate side chains, largely anchored to core proteins such as syndecan-1 and glypican-1, constitute the dominant glycosaminoglycan species within this layer, and their proteolytic or enzymatic cleavage during acute inflammatory states releases soluble heparan sulphate fragments and shed syndecan-1 ectodomain into the systemic circulation [2]. Because this shedding process occurs early and in proportion to the severity of the inflammatory and coagulopathic insult, circulating heparan sulphate and syndecan-1 have attracted sustained interest as candidate biomarkers of endothelial injury in sepsis, potentially offering earlier and more mechanistically specific information than conventional organ-dysfunction scores.

The conceptual case for glycocalyx-derived biomarkers rests on a well-described chain of pathophysiology. Sepsis-associated release of inflammatory cytokines, activation of matrix metalloproteinases and heparanase, and generation of reactive oxygen species act in concert to degrade the glycocalyx, exposing adhesion molecules, promoting capillary leak, and disrupting the endothelial glycocalyx's normal barrier and anticoagulant functions [3]. This degradation is not a passive epiphenomenon of critical illness but has been proposed as an active contributor to the vascular leak, interstitial oedema, and microcirculatory dysfunction that characterise septic shock, prompting calls to consider the glycocalyx a therapeutic as well as a diagnostic target [4]. Early clinical studies documented that plasma concentrations

of glycosaminoglycan fragments, including hyaluronan alongside heparan sulphate, rise substantially in patients with septic shock relative to healthy controls, accompanied by measurable derangements in plasma viscosity and hemorheology consistent with a systemic, rather than purely local, endothelial insult [5]. This narrative review synthesises the published literature addressing four interrelated aspects of heparan sulphate and syndecan-1 biology in sepsis: the biological basis for their use as biomarkers of endothelial injury, their association with disease severity and organ dysfunction, their prognostic and mortality-predictive value across cohort studies and meta-analyses, and the more recent controlled and mechanistic evidence bearing on causality and modifiability of glycocalyx shedding during sepsis resuscitation.

Biological Basis and Early Evidence for Glycocalyx-Derived Biomarkers

The physiological architecture of the endothelial glycocalyx was systematically characterised by Reitsma and colleagues, who described its composition of membrane-bound and secreted proteoglycans, its thickness of up to several hundred nanometres in the intact microcirculation, and its function as a dynamic mechanosensor and molecular sieve regulating transvascular flux [1]. This structural framework provided the foundation for subsequent work proposing that sepsis-induced degradation of the glycocalyx represents a unifying mechanism linking systemic inflammation to the vascular leak, interstitial oedema, and impaired microvascular perfusion observed clinically in septic shock, with Chelazzi and colleagues emphasising those consequences for vascular permeability specifically [3]. Burke-Gaffney and Evans, in an editorial accompanying early clinical glycocalyx studies, argued that clinicians should not overlook the glycocalyx as a potential diagnostic and therapeutic target in sepsis, noting that its degradation products were measurable in the systemic circulation using assays already validated for other glycosaminoglycan applications [4].

Building on this rationale, Sallisalmi and colleagues undertook one of the earlier clinical characterisations of glycosaminoglycan shedding in human septic shock, demonstrating markedly elevated plasma hyaluronan concentrations alongside altered whole-blood and plasma viscosity in patients sampled on the first and fourth days of treatment, findings interpreted as evidence of a systemic rather than purely microvascular derangement of the endothelial surface layer [5]. Uchimido, Schmidt, and Shapiro subsequently reviewed the accumulating evidence for glycocalyx components, including heparan sulphate and shed syndecan-1, as diagnostic biomarkers in sepsis, cataloguing the range of assay platforms used across studies and highlighting that, despite methodological heterogeneity, elevated circulating glycocalyx fragments were a near-universal finding across cohorts of septic and critically ill patients compared with healthy or non-septic controls [2]. Together, this body of foundational work established both the biological plausibility and the empirical basis for treating heparan sulphate and syndecan-1 as circulating readouts of endothelial glycocalyx injury, setting the stage for their evaluation as markers of disease severity.

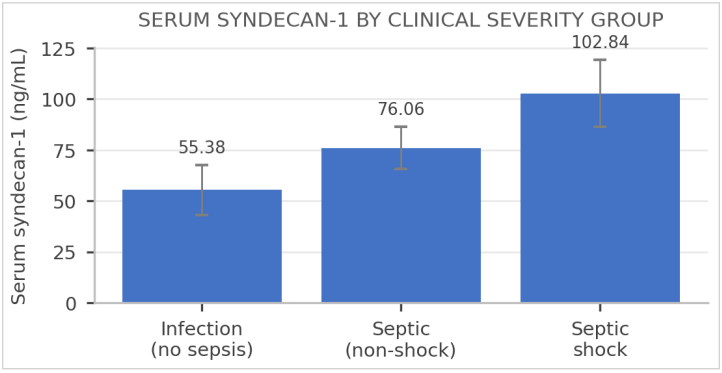
Association with Severity of Illness and Organ Dysfunction

A substantial body of clinical research has examined whether circulating glycocalyx degradation products track the severity of sepsis and the extent of concurrent organ dysfunction. Suzuki and colleagues measured serum syndecan-1 in a cohort of critically ill patients and found that concentrations correlated with validated organ-dysfunction scoring, concluding that syndecan-1 reflects the degree of multi-organ dysfunction present at the time of sampling rather than being specific to any single failing organ system [6]. Complementary work by Zhou and colleagues reported that endothelial dysfunction-related biomarkers, including syndecan-1 and soluble thrombomodulin, were elevated in proportion to sepsis severity and demonstrated discriminatory value for identifying incident sepsis among critically ill patients, with syndecan-1 outperforming soluble thrombomodulin in this diagnostic role [7].

Representative studies linking circulating syndecan-1 or heparan sulphate fragments to sepsis severity and organ dysfunction.

Study	Population/design	Biomarker finding	Association reported
Zhou et al. 2022	105 patients: infection (n=28), septic non-shock (n=31), septic shock (n=46)	Syndecan-1 55.38±12.34 (infection) to 102.84±16.53 ng/mL (septic shock)	AUC 0.95 for sepsis and for septic shock, both P<0.0001
Suzuki et al. 2021	94 critically ill patients, 831 serial blood samples	SDC-1 quartiles 16.67-318.11 ng/mL; AST/ALT /creatinine/BUN correlations	HR 2.08 (95% CI 1.24-3.49) for mortality per SDC-1 rise 24.23→143.91 ng/mL
Hatanaka et al. 2021	Population study, suspected sepsis requiring ICU care	Elevated circulating syndecan-1	Predicted persistent thrombocytopenia and lethal outcome
Smart et al. 2018	Sepsis due to pneumonia, syndecan-1 vs endocan compared	Syndecan-1 correlated with neutrophil activation markers	Stronger predictor of respiratory failure than endocan
Kajita et al. 2021	Septic shock, serial syndecan-1 sampling	Longitudinal syndecan-1 trajectory (not single value)	Predicted ARDS risk and cumulative fluid balance

Mean (± SD) serum syndecan-1 concentration by clinical severity group among patients with suspected infection, non-shock sepsis, and septic shock, illustrating a graded rise in glycocalyx shedding with worsening severity (Zhou et al., 2022).



Coagulation-related organ dysfunction has been a particular focus of this severity literature. Ostrowski and colleagues, in a prospective study of patients with severe sepsis, found that higher circulating concentrations of endothelial injury biomarkers were independently associated with impaired clot formation on viscoelastic coagulation testing, linking glycocalyx degradation

mechanistically to the sepsis-associated coagulopathy phenotype [8]. Hatanaka and colleagues extended this line of investigation in a population study of patients with suspected sepsis requiring intensive care, reporting that elevated circulating syndecan-1 predicted the subsequent development of persistent thrombocytopenia as well as lethal outcome, implicating glycocalyx shedding in the pathogenesis of sepsis-associated thrombocytopenia and positioning syndecan-1 as a marker bridging endothelial and haemostatic dysfunction [9]. In the pulmonary domain, Smart and colleagues compared syndecan-1 with the endothelial biomarker endocan in patients with sepsis due to pneumonia and found that syndecan-1 was the stronger predictor of subsequent respiratory failure, correlating significantly with markers of neutrophil activation and supporting a specific role for glycocalyx injury in the pathogenesis of septic acute respiratory failure [10]. A longitudinal study by Kajita and colleagues in patients with septic shock further showed that the trajectory of syndecan-1 over the early clinical course, rather than a single baseline value, predicted the subsequent development of acute respiratory distress syndrome and was associated with cumulative fluid balance, suggesting that repeated sampling may capture prognostically relevant dynamic information not evident from a single measurement [11].

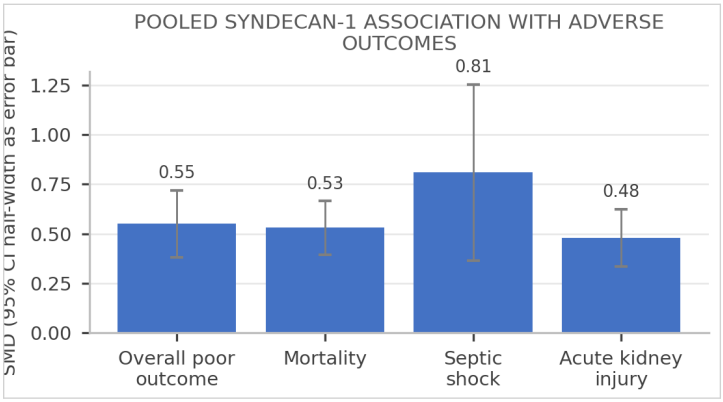
Prognostic Value for Mortality and Clinical Outcomes

Beyond associations with concurrent organ dysfunction, a considerable literature has directly examined whether heparan sulphate and syndecan-1 predict mortality and other patient-centred outcomes in sepsis. Two independent meta-analyses have now synthesised this evidence base. Sun and colleagues pooled data across eleven studies comprising 2,318 participants and found that elevated baseline syndecan-1 concentrations were consistently associated with a greater risk of sepsis-related complications and death, supporting the biomarker's prognostic utility across heterogeneous clinical settings and assay platforms [12]. Fernández-Sarmiento and colleagues conducted a complementary systematic review and meta-analysis of biomarkers of glycocalyx injury and endothelial activation, likewise concluding that elevated glycocalyx and endothelial activation markers, syndecan-1 prominent among them, were significantly associated with adverse clinical outcomes in patients with sepsis, reinforcing the reproducibility of this prognostic signal across the published cohort literature [13].

Meta-analyses and large cohort studies of glycocalyx biomarkers and clinical outcomes in sepsis.

Study	Design	Metric	Principal finding
Sun et al. 2022	Meta-analysis, 11 studies, n=2,318	SMD (95% CI)	Mortality 0.53 (0.40-0.67); septic shock 0.81 (0.36-1.25); AKI 0.48 (0.33-0.62)
Fernández-Sarmiento et al. 2023	Systematic review and meta-analysis	Pooled association	Glycocalyx/endothelial activation markers significantly associated with adverse outcomes
Piotti et al. 2021 (ALBIOS substudy)	Prospective substudy, septic shock	Syndecan-1, S1P, soluble VE-cadherin	Endothelial damage markers tracked with clinical severity
Oshima et al. 2025 (CLOVERS substudy)	Multicenter phase 3 randomized trial substudy	Glycocalyx fragment concentration	Degradation predicted adverse outcome independent of fluid strategy

Pooled standardized mean difference (SMD) in syndecan-1 concentration between patients with and without the indicated adverse outcome, from an 11-study, 2,318-patient meta-analysis (Sun et al., 2022). Values above zero indicate higher syndecan-1 in the adverse-outcome group; error bars show 95% confidence intervals.



Individual prospective cohort studies have added granularity to these pooled findings. Piotti and colleagues, in a substudy of the ALBIOS trial population with septic shock, demonstrated that circulating syndecan-1 alongside sphingosine-1-phosphate and soluble VE-cadherin provided evidence of endothelial damage that tracked with clinical severity, situating syndecan-1 within a broader panel of endothelial injury markers rather than as an isolated signal [14]. Most recently, Oshima and colleagues undertook a large-scale analysis nested within the CLOVERS trial, a multicentre, phase 3, randomised trial of resuscitation strategies in septic shock, and found that greater endothelial glycocalyx degradation, evidenced by higher circulating glycocalyx fragment concentrations, was associated with adverse outcomes independent of the randomised fluid strategy, providing some of the most rigorously controlled prognostic evidence available to date for glycocalyx biomarkers in sepsis [15]. Across this literature, the prognostic association between circulating heparan sulphate or syndecan-1 and mortality appears robust to variation in patient population, biomarker assay, and study design, even as absolute biomarker thresholds and effect sizes vary considerably between cohorts.

Mechanistic and Resuscitation-Related Considerations

A more recent strand of research has probed whether glycocalyx shedding is a passive marker of illness severity or an actively modifiable process, with particular attention to the volume of intravenous fluid administered during resuscitation. Hippensteel and colleagues reported that the volume of intravenous fluid given during sepsis resuscitation was independently associated with the degree of glycocalyx degradation, as reflected by circulating heparan sulphate fragment concentrations, raising the possibility that fluid administration itself contributes to endothelial injury in septic patients [16]. This finding was not, however, uniformly replicated: Macdonald and colleagues, studying patients undergoing resuscitation for sepsis in the emergency department, found no significant association between intravenous fluid volume and endothelial glycocalyx shedding, suggesting that the relationship between resuscitation practice and glycocalyx injury may be more complex or context-dependent

than initially proposed [17]. The CLOVERS trial substudy by Oshima and colleagues, benefiting from randomised allocation to liberal crystalloid versus early vasopressor strategies, offers the most direct test of this question to date, and its finding that glycocalyx degradation predicted outcome independent of assigned fluid strategy suggests that the underlying inflammatory and enzymatic drivers of shedding, rather than fluid volume per se, may be the dominant determinant of glycocalyx injury in this population [15].

Age-related and enzymatic mechanisms of glycocalyx breakdown have also received recent attention. Sallee and colleagues examined circulating heparanase-1 activity, the principal enzyme responsible for endothelial heparan sulphate cleavage, across the age spectrum in sepsis and found age-related differences in enzymatic activity that correlated with markers of systemic vascular endotheliopathy, implicating heparanase as a mechanistic link between patient age, a well-established sepsis risk factor, and the magnitude of glycocalyx injury [18]. A broader synthesis by Saavedra-Torres and colleagues situated glycocalyx shedding within the wider trajectory from endothelial pathophysiology to microvascular collapse in sepsis, cataloguing the mechanistic biomarkers implicated at each stage of this process and arguing for a staged conceptual model linking initial enzymatic shedding to progressive microcirculatory failure and, ultimately, organ dysfunction [19]. Together, these mechanistic and interventional studies indicate that while circulating heparan sulphate and syndecan-1 reliably track the presence and severity of endothelial injury in sepsis, the causal contribution of specific clinical exposures, particularly resuscitation fluid volume, to that injury remains only partially resolved and is an active area of investigation.

Conclusion

The cumulative literature reviewed here supports circulating heparan sulphate fragments and shed syndecan-1 as biologically plausible and clinically informative biomarkers of endothelial glycocalyx injury in sepsis. From the initial structural characterisation of the glycocalyx and early demonstrations of glycosaminoglycan shedding in septic shock [1,5], through consistent associations with organ dysfunction across respiratory, haemostatic, and multi-organ domains [6,9,10,11,7], to reproducible prognostic associations with mortality confirmed in independent meta-analyses and large trial-embedded cohorts [12,13,14,15], the evidence base has matured considerably over the past decade and a half. What remains less settled is the precise causal architecture linking clinical exposures, most notably resuscitation fluid volume, to the magnitude of glycocalyx shedding, an area in which controlled and randomised evidence has begun to emerge but has not yet yielded a unified mechanistic account [16,17,18,19]. As assay standardisation improves and prospective cohorts increasingly embed glycocalyx biomarkers within randomised resuscitation trials, heparan sulphate and syndecan-1 are well positioned to move from research tools toward biomarkers that could inform risk stratification and, potentially, glycocalyx-protective resuscitation strategies in early sepsis care.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Davide Ricci conceived the review, conducted the literature search, and drafted the manuscript. Marija Novak contributed to the literature screening, extraction of quantitative findings from the primary studies, and critically revised the manuscript for important intellectual content. Niamh Murphy contributed additional immunological and mechanistic context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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