Case Study
ISSN: 3051-8822
Journal homepage: https://www.harrisonacademicpress.com/index.php/IJCEHM
International Journal of Clinical and Experimental Human Medicine

Harrison Academic Press

Prognostic Value of Serum Heparanase Levels in Patients with Septic Shock

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ABSTRACT

Background: Septic shock carries persistently high mortality, and the microcirculatory failure that defines the syndrome is inseparable from loss of endothelial glycocalyx integrity. Heparanase, the principal mammalian enzyme capable of cleaving heparan sulfate, has emerged as both a mechanistic driver of glycocalyx degradation and a candidate circulating biomarker of severity in sepsis. Objective: This narrative review synthesizes the preclinical and clinical literature on heparanase biology in sepsis and evaluates the evidence for circulating heparanase as a prognostic biomarker in septic shock. Methods: We reviewed mechanistic studies establishing heparanase's role in pulmonary, renal, and neurological injury during sepsis; clinical studies measuring circulating heparanase level, procoagulant activity, or enzymatic activity in septic and septic shock cohorts and relating these measures to severity and mortality; comparative evidence involving syndecan-1 and other glycocalyx biomarkers; and intervention studies of pharmacological heparanase inhibition. Findings: Heparanase is activated by tumor necrosis factor-alpha and drives glycocalyx degradation, neutrophil adhesion, and organ injury across the lung, kidney, gut, heart, and brain in experimental sepsis. Clinical studies report associations between circulating heparanase-related measures and illness severity, organ-specific injury, and mortality, although assay methodology and the direction of cross-sectional associations vary across cohorts. Heparanase is mechanistically upstream of syndecan-1 shedding, and low molecular weight heparin, which inhibits heparanase in addition to its anticoagulant activity, has improved gastrointestinal and cardiac outcomes in small clinical studies of septic patients. Conclusions: Serum heparanase is a biologically well-justified and increasingly evidenced, but not yet fully validated, prognostic biomarker in septic shock. Large, prospective, septic shock-specific cohorts using a standardized assay and serial sampling, benchmarked against syndecan-1 and standard severity scores, are needed before heparanase measurement can be recommended for routine prognostic use.

Keywords: *heparanase; septic shock; endothelial glycocalyx; prognostic biomarker; heparan sulfate*

Citation: Makinen E, Papas M and Gruber J (2024) Prognostic Value of Serum Heparanase Levels in Patients with Septic Shock. Int J Clin Exp Hum Med, 2(1): 01-06.

DOI: 10.5281/zenodo.22644156

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Article History: *Received 7 January 2024 | Accepted 19 April 2024 | Published 24 July 2024*

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Introduction

Septic shock remains one of the most lethal syndromes encountered in critical care, accounting for a substantial share of the roughly 48.9 million incident sepsis cases and 11 million sepsis-related deaths estimated worldwide each year, with mortality that has fallen only modestly despite decades of trial activity in fluid resuscitation, vasopressor strategy, and source control [1]. The Sepsis-3 consensus definitions reframed sepsis as a dysregulated host response to infection producing life-threatening organ dysfunction, and defined septic shock as the subset of sepsis in which profound circulatory, cellular, and metabolic derangements substantially increase mortality, operationalized clinically by vasopressor-dependent hypotension and elevated serum lactate despite adequate volume resuscitation [2,3]. This framework, precisely because it is built around circulatory failure, has intensified interest in the vascular endothelium itself as both a mechanistic driver and a potential source of prognostic biomarkers in septic shock, since the microcirculatory collapse that defines the syndrome is inseparable from loss of endothelial barrier integrity.

Central to this vascular injury is the endothelial glycocalyx, a carbohydrate-rich layer coating the luminal surface of vascular endothelium that under physiological conditions regulates vascular permeability, mechanotransduction, leukocyte adhesion, and coagulation [4]. The glycocalyx is built substantially from heparan sulfate proteoglycans anchored to the endothelial

membrane, and its structural integrity depends on the balance between heparan sulfate biosynthesis and its enzymatic degradation [5]. Heparanase is the principal mammalian endo-β-D-glucuronidase capable of cleaving heparan sulfate side chains, and it is unusual among glycocalyx-degrading enzymes in functioning both as a proteolytic sheddase and, independent of its catalytic activity, as a signaling molecule that can directly modulate gene expression, cytoskeletal organization, and cytokine release in the cells that express it [6]. This dual enzymatic and non-enzymatic behavior is what elevates heparanase from a passive marker of glycocalyx injury to an active participant in the amplification of the septic inflammatory and coagulopathic cascade, a distinction that underlies much of the contemporary interest in measuring it in critically ill patients.

The mechanistic case for heparanase as a mediator, rather than a bystander, of septic organ injury was established in a series of murine and translational studies showing that tumor necrosis factor-α-dependent activation of endothelial heparanase drives pulmonary glycocalyx degradation, exposes adhesion molecules to circulating neutrophils, and precipitates acute lung injury, with parallel elevation of heparanase activity and lung tissue heparanase content in human septic patients with respiratory failure [7]. Subsequent work extended this mechanism to the kidney, where heparanase activation early in murine sepsis was shown to mediate proteinuria, tubular injury, and glomerular endothelial dysfunction independent of hypotension [8], and to the central nervous system, where heparanase-generated circulating heparan sulfate fragments were shown to cross an already compromised blood-brain barrier and to directly impair hippocampal synaptic function, offering a candidate mechanism for septic encephalopathy [9]. Together, this body of preclinical evidence positions heparanase not merely as a passive readout of vascular injury but as a proximate, druggable driver of the multi-organ dysfunction that determines outcome in septic shock, a rationale that has since motivated a growing, still heterogeneous clinical literature examining circulating heparanase as a prognostic biomarker.

This review synthesizes that literature across four themes: the biology linking heparanase to glycocalyx degradation and endothelial dysfunction in sepsis; the clinical studies that have measured circulating heparanase or heparanase activity in septic and septic shock cohorts and related these levels to severity and mortality; the comparative standing of heparanase alongside other candidate glycocalyx biomarkers, principally syndecan-1; and the emerging evidence, still preliminary, that pharmacological heparanase inhibition may translate prognostic association into a therapeutic target in septic shock and its organ-specific complications.

Heparanase Biology and the Endothelial Glycocalyx in Sepsis

Heparanase is synthesized as a latent 65 kDa proenzyme that is proteolytically processed into an active heterodimer within lysosomes and then trafficked to the cell surface and extracellular space, where it retains the capacity to cleave heparan sulfate at a limited number of intrachain sites, releasing bioactive fragments of 10 to 20 saccharide units [6]. Under homeostatic conditions its activity is tightly restrained, but tumor necrosis factor-α, generated in abundance during sepsis, upregulates both heparanase expression and its enzymatic activation, establishing a direct inflammatory-to-enzymatic axis linking the cytokine storm of sepsis to structural degradation of the vascular lining [7]. Because heparan sulfate proteoglycans constitute the majority of the glycocalyx's negatively charged, water-retentive matrix, their heparanase-mediated cleavage collapses the layer's thickness and charge density, exposing underlying adhesion molecules such as intercellular adhesion molecule-1 and P-selectin that are otherwise sterically shielded, and thereby converting a quiescent endothelium into one that is adhesive to circulating neutrophils and platelets [7,4].

The consequences of this degradation extend well beyond localized leukocyte adhesion. Because glycocalyx heparan sulfate also modulates endothelial mechanotransduction and nitric oxide synthase activity, its loss impairs flow-dependent vasodilation and contributes to the microcirculatory heterogeneity that is a hallmark of septic shock, in which some capillary beds remain patent while adjacent beds are functionally obstructed despite normalized macrocirculatory pressures [4]. The glycocalyx additionally sequesters antithrombin III and tissue factor pathway inhibitor and normally suppresses local thrombin generation; its heparanase-mediated shedding therefore also promotes a locally procoagulant endothelial phenotype, providing one mechanistic bridge between glycocalyx injury and the disseminated microvascular thrombosis observed in severe septic shock [5]. A comprehensive review of heparan sulfate and heparan sulfate-binding proteins in sepsis catalogued this pleiotropic role, noting that heparan sulfate fragments liberated by heparanase are not inert cleavage debris but themselves function as damage-associated molecular patterns capable of engaging toll-like receptor 4 and amplifying the innate immune response, creating a feed-forward loop in which glycocalyx degradation begets further inflammation and further degradation [5].

This feed-forward relationship helps explain why heparanase-mediated glycocalyx injury has been implicated across multiple organ systems in sepsis rather than being confined to a single vascular bed. In the kidney, heparanase activation was shown to be necessary for the proteinuria and glomerular endothelial cell injury that develop within hours of endotoxin or cecal ligation and puncture challenge in mice, with heparanase-deficient animals substantially protected from early septic renal dysfunction independent of blood pressure changes, establishing a causal, not merely correlative, role for the enzyme in septic acute kidney injury [8]. A dedicated review of heparanase in sepsis-associated acute kidney injury subsequently synthesized this and related mechanistic work, framing heparanase inhibition as a plausible renoprotective strategy distinct from hemodynamic optimization alone [10]. In the myocardium, a parallel review catalogued evidence that heparanase-mediated glycocalyx and extracellular matrix degradation contributes to septic cardiomyopathy through disruption of cardiomyocyte membrane integrity, calcium handling, and coronary microvascular barrier function, again nominating heparanase as a mechanistic node common to the multi-organ phenotype of septic shock rather than a marker specific to any one organ [11]. This convergence of organ-specific mechanistic literatures onto a single enzyme is the principal reason circulating heparanase has been pursued as a candidate prognostic biomarker capable of integrating global endothelial injury burden into a single measurable value.

Circulating Heparanase as a Marker of Severity and Outcome in Septic Shock

Direct clinical measurement of circulating heparanase in septic

patients has produced a literature that is smaller than the mechanistic literature but increasingly consistent in linking heparanase-related measures to disease severity, even as the specific assay used and the direction of the observed association have varied across studies. Matan and colleagues measured plasma heparanase level and heparanase procoagulant activity, an assay reflecting heparanase's capacity to promote tissue factor pathway inhibitor-dependent coagulation, in 21 patients with severe sepsis compared with 35 healthy controls, and found that both measures were significantly reduced in patients relative to controls on day one ($P < .0001$ for each), a finding the authors interpreted as reflecting consumption or altered compartmentalization of circulating heparanase during the acute procoagulant phase of severe sepsis rather than the systemic elevation that intuition might predict [12]. Notably, in the same cohort, a day one heparanase procoagulant activity threshold of 350 ng/mL yielded a negative predictive value of 89% for severe sepsis, and the trajectory of heparanase procoagulant activity between day one and day seven correlated with the change in APACHE II score over the same interval ($r = .66$, $P = .007$), suggesting that while cross-sectional heparanase levels may fall during acute severe sepsis, their dynamic trajectory over the first week tracks recovery or deterioration in a manner that could support prognostic use [12].

Representative clinical studies measuring circulating heparanase or heparanase-related activity in sepsis and septic shock cohorts cited in this review.

Study	Assay / cohort	Design	Principal finding
Matan et al. 2018	Heparanase level and procoagulant activity; 21 severe sepsis vs 35 controls	Case-control, days 1 and 7	Both measures significantly reduced in patients (P<.0001); day 7 trajectory correlated with APACHE change (r=.66, P=.007)
Sallee et al. 2026	Plasma heparanase-1 activity; adult (n=16) vs pediatric (n=10) sepsis	Comparative cohort	Adult activity ~10-fold higher than pediatric (1256 vs 116 U/mL, P<.001); higher in adult non-survivors
Chen et al. 2023	Serum heparanase; sepsis-associated acute gastrointestinal injury	Diagnostic accuracy study	AUC 0.9241 for injury severity, 93.68% sensitivity, 82.54% specificity
Chen et al. 2024 (Frontiers in Medicine)	Serum heparanase; 105 septic cardiomyopathy patients, LMWH vs standard care	Randomized clinical study	LMWH reduced heparanase, improved LVEF/FS/E-e', lowered 28-day mortality

By contrast, more recent work assaying heparanase-1 enzymatic activity directly, rather than procoagulant activity as a surrogate, has found circulating heparanase activity to be markedly elevated in septic patients and, within adults, higher still among those who die. Sallee and colleagues compared plasma heparanase-1 activity in adults and children with sepsis and found activity roughly ten-fold higher in septic adults than in septic children (median 1,256 U/mL versus 116 U/mL, $P < .001$), with adult non-survivors showing significantly higher heparanase-1 activity than adult survivors, even though control groups of both ages had similarly low baseline activity (49 versus 73 U/mL, $P = .258$) [13]. This age-related divergence was paradoxical in one respect: despite lower heparanase-1 activity, septic children in the same study exhibited greater endotheliopathy by other measures, including higher circulating angiopoietin-2 (4.48 ng/mL versus 1.79 ng/mL in adults), larger 24-hour declines in serum albumin, and higher organ failure scores (median 13 versus 6, $P < .001$), while mortality among the ten children studied was zero compared with 31% (5 of 16) among adults [13]. The authors reconciled this apparent discordance by demonstrating that circulating heparan sulfate in adults showed fewer heparanase-cleavable disaccharide sites than in children, consistent with greater prior enzymatic degradation in adults and an inverse relationship between residual cleavable substrate and measured heparanase-1 activity, implying that heparanase activity and cumulative glycocalyx injury are related but not interchangeable readouts, and that pediatric endotheliopathy in sepsis may proceed through heparanase-independent pathways to a greater degree than in adults [13].

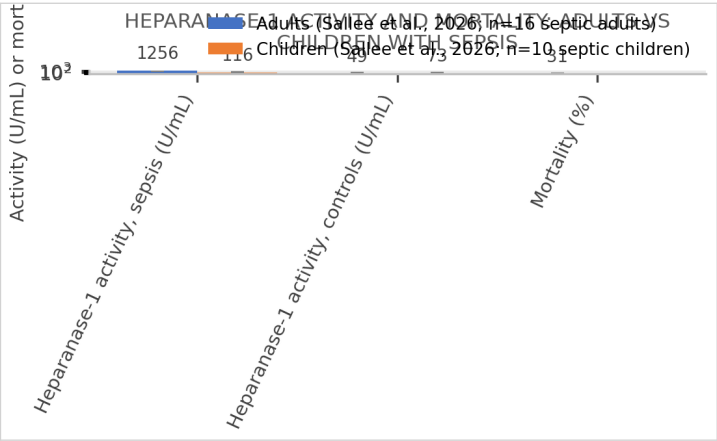
Complementary evidence for heparanase's severity association comes from a study explicitly targeting the intestinal vascular bed, in which Chen and colleagues measured serum heparanase in patients with sepsis-associated acute gastrointestinal injury and reported that heparanase discriminated injury severity with an area under the receiver operating characteristic curve of 0.9241, corresponding to 93.68% sensitivity and 82.54% specificity, a diagnostic performance exceeding that of intestinal fatty acid binding protein and D-lactate measured in the same cohort [14]. Taken together, these three clinical studies, despite differing in assay methodology, patient population, and even the direction of the cross-sectional heparanase-severity relationship reported by Matan and colleagues relative to Sallee and colleagues, converge on the conclusion that circulating heparanase-related measures carry information about disease severity and trajectory in sepsis and septic shock that is not fully captured by standard severity scores, while also underscoring that heparanase procoagulant activity, heparanase-1 enzymatic activity, and heparanase antigen level are related but non-equivalent assays whose comparability across studies remains incompletely established [12,13,14].

Heparanase Alongside Other Glycocalyx Biomarkers: Comparative Prognostic Standing

Heparanase does not stand alone as a candidate glycocalyx biomarker in sepsis, and its prognostic value is best interpreted in the context of the broader endothelial biomarker literature, in which syndecan-1, the principal transmembrane heparan sulfate proteoglycan shed from the endothelial surface, has accumulated the largest evidence base. A systematic review and meta-analysis pooling glycocalyx and endothelial biomarker studies in sepsis, including syndecan-1, heparan sulfate, and related markers, found that elevated glycocalyx degradation products were consistently associated with greater illness severity, need for vasopressor support, and mortality across the pooled cohorts, while also noting substantial heterogeneity in assay platforms, sampling time points, and case-mix that limits precise pooled effect estimates and complicates direct comparison between individual biomarkers such as heparanase and syndecan-1 [15]. This heterogeneity mirrors, at the level of a systematic review, the same methodological variability observed within the

heparanase-specific literature itself, and argues for standardization of assay methodology before circulating heparanase or any single glycocalyx marker can be adopted as a stand-alone prognostic test.

Circulating heparanase-1 activity and 28-day mortality in adults versus children with sepsis, illustrating the marked age-related divergence in enzyme activity and outcome reported in a comparative cohort study (Sallee et al., 2026).



Mechanistically, heparanase and syndecan-1 are closely linked rather than competing biomarkers, since heparanase cleavage of the heparan sulfate chains that decorate syndecan-1's core protein is one of the principal mechanisms by which syndecan-1 ectodomain shedding is triggered, meaning that elevated syndecan-1 in septic plasma is, in substantial part, a downstream consequence of heparanase activity rather than an independent injury signal [4,5]. This upstream-downstream relationship suggests a rationale for a combined biomarker approach: heparanase activity may better reflect the ongoing enzymatic drive toward glycocalyx degradation at the moment of sampling, while syndecan-1 concentration may better reflect the cumulative structural damage already sustained, an interpretation broadly consistent with the Sallee cohort's finding that heparanase-1 activity and residual heparan sulfate substrate availability moved in opposite, mechanistically coherent directions within the same patients [13]. Direct within-patient comparisons of heparanase and syndecan-1 measured contemporaneously in the same septic shock cohorts remain sparse in the published literature, and this absence is itself a notable gap, since establishing whether heparanase adds independent prognostic information beyond syndecan-1, or is instead redundant with it, is a prerequisite for any recommendation to measure both markers in clinical practice.

A further comparative consideration is organ specificity. Circulating heparanase has been most extensively validated as a severity marker in the gastrointestinal and pulmonary vascular beds, where its diagnostic performance for organ-specific injury has been directly quantified [14,7], whereas syndecan-1 has been studied across a broader range of septic phenotypes, including microcirculatory dysfunction assessed by sublingual video-microscopy and its association with fluid responsiveness [15]. Other heparan sulfate-derived measures, including plasma chondroitin sulfate, have separately been shown to track fluid resuscitation strategy effectiveness in septic patients, illustrating that the glycocalyx biomarker field is diversifying beyond heparanase and syndecan-1 into a panel of related but mechanistically distinct measures, any of which might ultimately prove more clinically actionable than heparanase alone, or might be combined with heparanase into a composite endotheliopathy score with superior prognostic discrimination to any single marker [5]. Until such panels are prospectively validated head-to-head in septic shock cohorts specifically, heparanase should be regarded as one strong, mechanistically well-justified candidate among a small family of related glycocalyx biomarkers rather than a validated stand-alone prognostic test ready for bedside adoption.

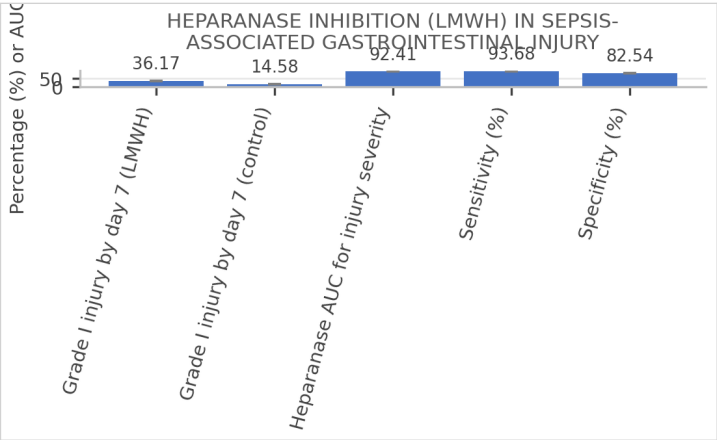
From Prognostic Marker to Therapeutic Target: Heparanase Inhibition in Septic Shock

The strongest evidence that circulating heparanase is not merely an epiphenomenal marker of septic vascular injury, but a proximate mediator of it, comes from intervention studies in which pharmacological heparanase inhibition has been shown to improve organ-specific outcomes. Low molecular weight heparin, in addition to its established anticoagulant activity, competitively inhibits heparanase by mimicking its heparan sulfate substrate, and this dual activity has been exploited in two clinical studies from the same research group examining heparanase-mediated organ injury in sepsis. In patients with sepsis-associated acute gastrointestinal injury, low molecular weight heparin treatment produced significantly lower serum heparanase, intestinal fatty acid binding protein, D-lactate, and syndecan-1 concentrations by treatment day seven compared with standard care, alongside a higher proportion of patients achieving grade I (mildest) gastrointestinal injury by day seven (36.17% versus 14.58% in controls) and favorable shifts in CD4/CD8 lymphocyte ratios and anticoagulant parameters [14]. In a subsequent randomized clinical study enrolling 105 patients with septic cardiomyopathy, low molecular weight heparin treatment over seven days produced significant improvements in left ventricular ejection fraction, fractional shortening, and diastolic function (E/e′), together with reductions in NT-proBNP, cardiac troponin I, heart-type fatty acid binding protein, interleukin-6, and tumor necrosis factor-α, shorter ICU stay, lower APACHE II and SOFA scores, and a significantly lower 28-day mortality rate relative to standard care, with the authors attributing the cardioprotective effect specifically to attenuation of heparanase-mediated endothelial glycocalyx degradation in the coronary microcirculation [16].

These clinical signals are reinforced by preclinical evidence for renal protection through heparanase inhibition: in a murine model, the heparanase inhibitor PG545 attenuated proteinuria, tubular injury, and inflammatory infiltration following induced acute kidney injury, providing direct causal support, beyond the sepsis-specific renal work of Lygizos and colleagues, for heparanase as a druggable node in acute organ injury more broadly [17]. Most recently, a purpose-built small-molecule heparanase inhibitor was shown in an integrated preclinical and translational study to suppress the cytokine storm characteristic of severe sepsis and to improve survival in murine sepsis models by a mechanism explicitly linked to preservation of heparan sulfate integrity, representing a first step toward heparanase-targeted agents developed specifically for sepsis rather than repurposed from anticoagulant or oncology indications [18]. Considered together, this cluster of studies transforms the clinical significance of circulating heparanase measurement: if pharmacological heparanase inhibition can improve gastrointestinal, cardiac, and renal outcomes in sepsis, then serum heparanase is a plausible candidate not only for prognostic stratification but also for treatment-response monitoring and, potentially, for enrichment of future septic shock

trials to patients whose organ injury is heparanase-driven and therefore most likely to benefit from heparanase-directed therapy.

Reported outcomes of low molecular weight heparin (heparanase-inhibiting) treatment versus standard care in sepsis-associated acute gastrointestinal injury, including serum heparanase suppression and the proportion of patients achieving the mildest (grade I) injury grade by treatment day 7 (Chen et al., 2023).



Important limitations temper this optimism. The gastrointestinal and cardiomyopathy intervention studies were conducted by overlapping investigator groups using low molecular weight heparin, an agent with substantial anticoagulant activity independent of heparanase inhibition, so that attribution of the observed benefit specifically to heparanase inhibition, as opposed to the drug's broader antithrombotic and anti-inflammatory effects, cannot be fully disentangled without a heparanase-selective comparator arm [14,16]. Neither study was conducted in a population restricted to septic shock as distinct from sepsis more broadly, and the reduction in 28-day mortality reported in the cardiomyopathy trial, while striking, awaits independent replication in a larger, multicenter septic shock cohort before it can inform practice [16]. Nonetheless, the consistency of direction across gastrointestinal, cardiac, and renal organ systems, together with the mechanistic depth of the underlying heparanase biology, makes serum heparanase among the more mechanistically credible glycocalyx biomarkers currently under study in septic shock.

Conclusion

The literature reviewed here supports a coherent, if still incompletely validated, case for serum heparanase as a prognostic biomarker in septic shock. Mechanistic studies establish heparanase as a tumor necrosis factor-α-responsive enzyme that actively drives pulmonary, renal, and neurological injury through glycocalyx degradation and generation of bioactive heparan sulfate fragments, rather than serving merely as a passive marker of endothelial damage [7,8,9,6]. Clinical studies measuring circulating heparanase-related parameters in septic and septic shock cohorts have consistently found associations with illness severity, organ-specific injury, and mortality, even though the specific assay, direction of association, and patient population have varied enough across studies that pooled quantitative synthesis remains premature [12,13,14,15]. Heparanase's mechanistic and, increasingly, therapeutic relationship to syndecan-1 and other glycocalyx biomarkers suggests it is best considered as one component of a future composite endotheliopathy panel rather than a stand-alone test, and the encouraging early evidence that heparanase inhibition improves gastrointestinal, cardiac, and renal outcomes in sepsis strengthens the case that heparanase measurement has genuine treatment-relevant, and not merely descriptive, value [14,16,17,18]. What is still needed is a large, prospective, septic shock-specific cohort study using a single standardized heparanase assay, sampled serially rather than at a single time point, and analyzed alongside syndecan-1 and clinical severity scores, to establish whether serum heparanase adds independent prognostic discrimination to established tools such as the Sequential Organ Failure Assessment score and lactate clearance. Until that evidence accumulates, serum heparanase should be regarded as a biologically compelling and clinically promising, but not yet practice-ready, prognostic biomarker in septic shock.

Acknowledgements

The authors thank colleagues at the Department of Intensive Care Medicine, University of Helsinki, Helsinki, Finland, the Department of Clinical Biochemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece, and the Department of Infectious Diseases, University of Innsbruck, Innsbruck, Austria for helpful discussions during preparation of this review.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Makinen E conceived the review, conducted the literature search, and drafted the manuscript. Papas M contributed to the literature screening and biochemical framing and critically revised the manuscript for important intellectual content. Gruber J contributed additional clinical infectious disease 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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