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Circulating Heparan Sulphate as a Predictor of Acute Kidney Injury in Critically Ill Septic Patients

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ABSTRACT

Background: Acute kidney injury (AKI) complicates a majority of intensive care unit admissions for sepsis and independently worsens survival, yet creatinine- and urine output-based diagnostic criteria detect renal injury only after substantial nephron damage has occurred. The endothelial glycocalyx, whose principal glycosaminoglycan constituent is heparan sulphate, is degraded early in sepsis by heparanase and related sheddases, releasing fragments into blood and urine that may report on renal microvascular injury before functional decline is evident. Objective: To synthesise the published literature on circulating and urinary heparan sulphate, and its surrogate shed syndecan-1, as predictors of AKI in critically ill septic patients. Methods: A narrative review of mechanistic, epidemiological, and clinical cohort studies addressing heparan sulphate biology, heparanase-mediated renal glycocalyx shedding, and the diagnostic and prognostic performance of heparan sulphate-related biomarkers for sepsis-associated AKI (SA-AKI). Findings: SA-AKI affects over 60% of septic intensive care admissions in contemporary multicentre cohorts and carries mortality risk that scales with injury severity. Heparanase-mediated cleavage of renal endothelial heparan sulphate is detectable early in the septic course and precedes measurable changes in glomerular filtration. Cohort studies report that circulating syndecan-1 and heparin-binding protein independently predict incident AKI and need for kidney support therapy, with areas under the receiver operating characteristic curve (AUC) of 0.66-0.72 for single markers, rising to 0.77-0.91 when combined with renal resistive index, angiopoietin-2, or organ-dysfunction scores. A large trial-embedded analysis of the CLOVERS trial demonstrated a graded, dose-dependent association between baseline plasma heparan sulphate and 90-day mortality (9.9% to 44.2% across tertiles) that was independent of randomised fluid resuscitation strategy. Conclusions: Circulating and urinary heparan sulphate constitute biologically plausible and empirically supported predictors of AKI in septic critical illness, with best performance achieved in multimarker combinations. Assay standardisation and interventional trials testing biomarker-guided management are needed before routine clinical adoption.

Keywords: *heparan sulphate; endothelial glycocalyx; sepsis-associated acute kidney injury; syndecan-1; heparanase*

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Introduction

Acute kidney injury (AKI) complicates a substantial proportion of admissions for sepsis and septic shock, and its onset independently worsens short- and long-term survival, prolongs organ support, and accelerates progression to chronic kidney disease among survivors [1,2]. Despite decades of biomarker research, clinicians remain largely dependent on serum creatinine and urine output to recognise sepsis-associated AKI (SA-AKI), both of which are late, functional readouts that change only after substantial nephron injury has already occurred [2]. This diagnostic lag has motivated a search for biomarkers reporting on the earlier structural events driving renal injury in sepsis, and one of the most biologically compelling candidates is the endothelial glycocalyx and its principal glycosaminoglycan constituent, heparan sulphate.

The endothelial glycocalyx is a carbohydrate-rich layer coating the luminal surface of vascular endothelium, in which heparan sulphate side chains anchored to syndecan and glypican core proteins constitute the dominant structural and functional component, regulating vascular permeability, mechanotransduction, and the endothelial anticoagulant surface [3]. The renal microvasculature and glomerular capillary wall are especially rich in this glycocalyx layer, where it contributes directly to the size- and charge-selective properties of the

filtration barrier, so that its degradation has consequences that extend beyond generalised capillary leak to a direct compromise of glomerular and peritubular capillary function [4,5]. During sepsis, a cascade of inflammatory mediators, proteases, and heparan-sulphate-specific endoglycosidases, chief among them heparanase-1, cleave this layer and release soluble heparan sulphate fragments into the systemic circulation and urine, providing a plausible mechanistic link between the biomarker and the renal injury it is proposed to predict [6,7].

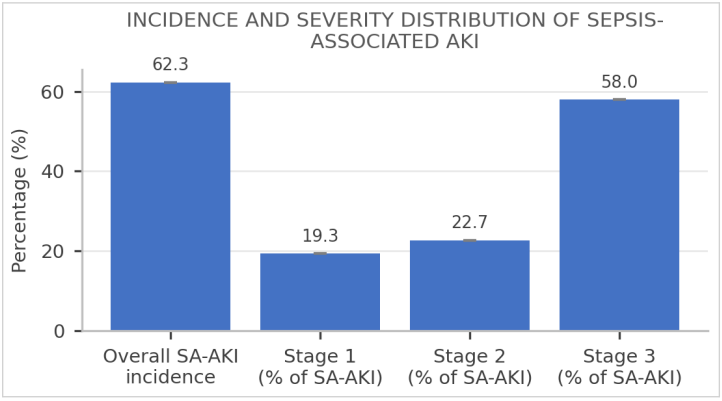
This narrative review synthesises the published literature specifically addressing circulating and urinary heparan sulphate, and its closely related surrogate shed syndecan-1, as predictors of AKI in critically ill septic patients. It proceeds through five thematic areas: the epidemiological burden of SA-AKI and the rationale for glycocalyx-based biomarkers; the biology of renal heparan sulphate shedding; the enzymatic and cellular mechanisms, centred on heparanase, that mediate this shedding in the septic kidney; the clinical cohort evidence quantifying the predictive performance of heparan sulphate and syndecan-1 for incident AKI and the need for kidney support therapy; and finally the more recent trial-embedded and resuscitation-related evidence bearing on the biomarker's robustness and remaining uncertainties. Distinct from prior reviews that have treated heparan sulphate primarily as a generic marker of endothelial injury in sepsis, this review focuses specifically on its performance as a predictor of renal outcomes.

Sepsis-Associated Acute Kidney Injury: Burden and the Case for Novel Biomarkers

Sepsis-associated AKI is now recognised as a distinct clinical phenotype rather than a simple consequence of global haemodynamic compromise, reflecting a convergence of inflammatory, microvascular, and cellular metabolic derangements within the kidney [2]. Contemporary multicentre data illustrate the scale of this problem: in a prospective observational cohort of 5,100 patients admitted to intensive care with sepsis across multiple centres in South Korea, Song and colleagues found that AKI, defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria, was confirmed in 62.3% of patients, with the majority of affected patients meeting criteria for KDIGO stage 3, the most severe category [8]. Higher-stage SA-AKI in this cohort carried a significantly elevated risk of in-hospital death compared with patients without AKI, whereas stage 1 injury alone did not, underscoring both the frequency and the outcome-relevance of more advanced renal injury in this population [8].

The persistence of this burden despite widespread clinical awareness reflects, in part, the limitations of the diagnostic tools in routine use. Serum creatinine is confounded by fluid balance, muscle mass, and the kinetics of renal clearance, so that a rise sufficient to meet KDIGO criteria typically follows substantial loss of functioning nephron mass by a lag of many hours [2]. Urine output criteria are similarly non-specific in the critically ill, where oliguria may reflect appropriate physiological water conservation as readily as tubular injury. These limitations create a diagnostic window, sometimes described as the "creatinine-blind" period, during which structural renal injury is already underway but undetectable by conventional means, and during which biomarker-guided intervention, whether through haemodynamic optimisation, avoidance of nephrotoxins, or early nephrology consultation, could plausibly alter trajectory [5].

Incidence and KDIGO stage distribution of sepsis-associated acute kidney injury (SA-AKI) among 5,100 critically ill septic patients in a multicenter, prospective South Korean cohort; stage percentages are expressed as a proportion of confirmed SA-AKI cases (Song et al., 2024).



It is against this backdrop that biomarkers of endothelial and glycocalyx injury have attracted particular interest. Because the renal microcirculation, and the glomerular capillary wall specifically, depends on an intact glycocalyx for both barrier function and local haemodynamic regulation, degradation of this layer represents a candidate upstream event that precedes and may causally contribute to the tubular and glomerular dysfunction that eventually manifests as a rise in creatinine [4]. Song and Goligorsky's group in particular argued that the glycocalyx functions as a literal "battleground" in sepsis-associated kidney injury, at which the competing forces of enzymatic degradation and reparative shedding-resistance determine whether microvascular integrity, and by extension renal function, is preserved [4]. Circulating fragments of heparan sulphate, released as a direct consequence of this degradation, therefore offer a mechanistically grounded candidate biomarker positioned temporally upstream of the functional decline captured by creatinine, motivating the substantial body of clinical evaluation reviewed in the sections that follow.

Endothelial Glycocalyx Biology and Renal Heparan Sulphate Shedding in Sepsis

The endothelial glycocalyx was systematically characterised as a dynamic, several-hundred-nanometre-thick layer of membrane-bound proteoglycans, glycosaminoglycans, and adsorbed plasma proteins coating the luminal endothelial surface, in which heparan sulphate chains anchored predominantly to syndecan-1 and glypican-1 core proteins constitute the dominant glycosaminoglycan species by mass [3]. This structural description provided the foundation for subsequent renal-specific work establishing that the glomerular endothelium and the fenestrated peritubular capillary network carry a particularly dense glycocalyx layer, one that contributes directly to the charge-selective component of glomerular filtration and to the regulation of peritubular oxygen and solute exchange [5]. Renal microvascular beds are therefore disproportionately vulnerable to the systemic glycocalyx-degrading milieu of sepsis, and glycocalyx loss within the kidney has been proposed as a proximate cause, rather than merely a correlate, of the microcirculatory dysfunction that characterises early septic AKI [4].

Clinical evidence for glycocalyx involvement in AKI extends across kidney disease more broadly, not only sepsis. Yilmaz and colleagues, reviewing the role of the endothelial glycocalyx in health and disease, noted that circulating concentrations of glycocalyx components including syndecan-1 and hyaluronan rise

progressively across stages of chronic kidney disease and are associated with the degree of proteinuria in diabetic nephropathy, indicating that glycocalyx integrity and renal barrier function are mechanistically linked across a spectrum of aetiologies beyond acute sepsis [5]. This broader nephrological literature strengthens the biological plausibility that heparan sulphate shedding in sepsis is not an epiphenomenon of systemic inflammation but reflects a process with direct consequences for renal microvascular and filtration function.

A comprehensive recent synthesis by Wang and colleagues situated glycocalyx degradation within the specific pathophysiological sequence of sepsis-induced AKI, cataloguing the principal enzymatic sheddases, the resulting soluble fragments detectable in blood and urine, and the downstream consequences for capillary leukocyte adhesion, microthrombosis, and loss of autoregulatory tone within the renal microcirculation [7]. This review emphasised that heparan sulphate shedding is temporally an early event, often detectable within hours of the onset of systemic inflammation and preceding measurable changes in glomerular filtration rate, reinforcing its candidacy as a predictive rather than purely correlative biomarker of impending renal injury [7]. Direct measurement of this shedding process in septic patients has been most rigorously accomplished using mass spectrometry-based quantification of urinary and plasma glycosaminoglycan fragments, an approach that established that indices of heparan sulphate, chondroitin sulphate, and hyaluronan fragmentation rise substantially in patients with septic shock relative to trauma intensive care unit controls, and that this fragmentation correlates with the subsequent development of renal dysfunction over the following 72 hours [9]. Together, this body of structural and mechanistic work establishes both the anatomic rationale and the temporal sequence required for heparan sulphate to function as a meaningful predictive, rather than merely descriptive, biomarker of AKI in sepsis.

Heparanase and Other Sheddases: Mechanistic Links Between Systemic Sepsis and Renal Glycocalyx Injury

Among the enzymes responsible for cleaving heparan sulphate from the endothelial surface, heparanase-1 has received the most sustained mechanistic attention specifically within the septic kidney. Lygizos and colleagues demonstrated in a murine model of sepsis that glomerular heparanase activity increases early in the disease course and contributes directly to septic renal dysfunction, using competitive heparanase inhibition to show that pharmacological blockade attenuated proteinuria and glomerular endothelial injury through mechanisms distinct from those operating in the sepsis-injured lung, indicating organ-specific regulation of heparanase-mediated glycocalyx loss [6]. This foundational experimental work has since been extended and reviewed by Li and colleagues, who catalogued the accumulating evidence implicating heparanase as a central mediator of sepsis-related AKI, describing its regulation by inflammatory cytokines, its action in exposing the underlying endothelial basement membrane to circulating leukocytes and complement, and its potential as both a biomarker and a therapeutic target in this setting [10].

A more recent line of investigation has examined whether heparanase activity itself, rather than only its downstream heparan sulphate fragment products, varies systematically with patient characteristics relevant to AKI risk. Sallee and colleagues measured circulating heparanase-1 activity across the age spectrum in patients with sepsis and found age-related differences in enzymatic activity that correlated with independent markers of systemic vascular endotheliopathy, suggesting that the well-established epidemiological association between advancing age and higher AKI risk in sepsis may be partly mediated by age-dependent variation in the enzymatic machinery governing glycocalyx shedding [11]. This finding adds a layer of mechanistic specificity to the biomarker literature, implying that circulating heparan sulphate concentrations reflect not only the severity of the inflammatory insult but also host-intrinsic factors that modulate the rate of its enzymatic release.

Principal enzymatic and cellular mediators implicated in renal endothelial glycocalyx and heparan sulphate degradation during sepsis.

Mediator	Cellular source	Proposed renal consequence	Key reference
Heparanase-1	Glomerular and tubular endothelium, activated leukocytes	Cleavage of heparan sulphate side chains; increased glomerular permeability and proteinuria	Lygizos et al. 2013; Li et al. 2023
Heparin-binding protein (azurocidin/CAP37)	Neutrophil azurophilic and secretory granules	Co-released marker of neutrophil-endothelial activation; independent AKI predictor	Pajenda et al. 2020
Matrix metalloproteinases	Endothelium, activated leukocytes	Degradation of core proteoglycan proteins anchoring heparan sulphate	Wang et al. 2025
Age-dependent heparanase activity	Systemic circulation	Modulates magnitude of endotheliopathy and AKI susceptibility with advancing age	Sallee et al. 2026

Heparanase does not act in isolation, and the broader sheddase repertoire relevant to renal glycocalyx injury includes matrix metalloproteinases, neutrophil elastase, and heparin-binding protein (HBP, also known as azurocidin or CAP37), a neutrophil granule protein that, while not itself a heparan-sulphate-cleaving enzyme, is co-released during neutrophil activation and has independently demonstrated diagnostic utility for sepsis-related AKI. Pajenda and colleagues reported that peak circulating HBP concentrations discriminated patients who developed AKI from those who did not, with an area under the receiver operating characteristic curve (AUC) of 0.67 at an optimal cut-off near 24 pg/mL, providing complementary evidence that the broader neutrophil-endothelial activation axis, of which heparanase-driven heparan sulphate shedding is one arm, carries predictive information for renal outcomes in sepsis [12]. Collectively, this mechanistic literature supports a model in which heparanase functions as the principal, but not sole, enzymatic driver converting systemic septic inflammation into measurable, kidney-relevant glycocalyx injury, with host factors such as age modulating the magnitude of this response.

Circulating and Urinary Heparan Sulphate as Predictors of Acute Kidney Injury: The Clinical Evidence

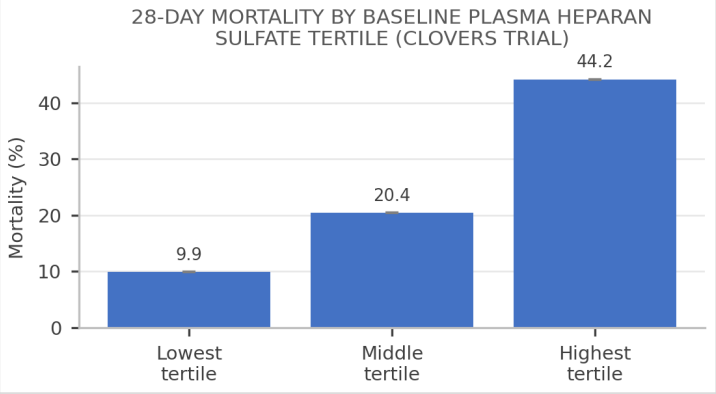
The clinical literature directly evaluating heparan sulphate and its principal surrogate, shed syndecan-1, as predictors of incident AKI in septic patients has grown substantially over the past decade, employing endpoints ranging from KDIGO-defined AKI onset to receipt of kidney support therapy. Schmidt and colleagues provided some of the earliest and most direct evidence,

demonstrating in a cohort of septic shock and acute respiratory distress syndrome patients that mass-spectrometry-quantified urinary glycosaminoglycan fragmentation, including heparan sulphate, predicted the development of renal dysfunction over the subsequent 72 hours as well as in-hospital mortality, independent of baseline severity of illness [9]. This early work has since been corroborated and extended by numerous single- and multi-marker cohort studies employing syndecan-1 as the principal circulating readout of heparan sulphate shedding.

Representative cohort studies quantifying the diagnostic or predictive performance (area under the receiver operating characteristic curve, AUC) of circulating heparan sulphate-related biomarkers for acute kidney injury or kidney support therapy in sepsis.

Study	Biomarker(s)	Population	Outcome and AUC
Pajenda et al. 2020	Peak heparin-binding protein	Mixed critically ill ICU cohort	AKI: AUC 0.67 (cut-off ~23.9 pg/mL)
Canbaz et al. 2025	Serum syndecan-1 (SDC1); SDC1+SOFA	Prospective septic ICU cohort	AKI: AUC 0.659 (SDC1 alone), 0.770 (SDC1+SOFA); RRT: AUC 0.715
Zhang et al. 2025	Plasma syndecan-1 + renal resistive index	Prospective septic ICU cohort, n=80	SA-AKI: AUC 0.680 (SDC1 alone), 0.859 combined (sensitivity 87.8%, specificity 74.4%)
Salmito et al. 2024	Syndecan-1 + angiopoietin-2 + clinical model	ICU cohort with KDIGO stage 2 AKI, n=127	Kidney support therapy within 72h: AUC 0.87 (SDC1 alone), 0.91 (biomarkers+clinical model)

28-day mortality by baseline plasma heparan sulfate tertile among 574 patients with septic shock enrolled in the CLOVERS trial, illustrating a graded, dose-dependent association between circulating heparan sulfate and mortality independent of randomized fluid resuscitation strategy (Oshima et al., 2025).



Canbaz and colleagues, in a prospective cohort study of septic intensive care unit patients evaluating multiple pathophysiologically distinct biomarkers for renal outcomes, found that serum syndecan-1 independently predicted both AKI (AUC 0.659; odds ratio 1.201 per unit increase) and subsequent need for renal replacement therapy (AUC 0.715; odds ratio 1.260), with predictive performance improving substantially when syndecan-1 was combined with the Sequential Organ Failure Assessment score (AUC 0.770 for AKI) [13]. This study directly compared syndecan-1 against neutrophil gelatinase-associated lipocalin (NGAL), a more established AKI biomarker, and found that although NGAL also discriminated AKI (AUC 0.666), only syndecan-1 remained independently associated with renal outcomes after multivariable adjustment, positioning it as the more robust of the two candidate markers in this cohort [13]. Complementary evidence in a paediatric septic population was provided by Semedi and colleagues, who demonstrated that urinary syndecan-1 had validity as a predictor of AKI in children with sepsis, extending the biomarker's evaluated age range beyond the adult-predominant literature [14]. Syndecan-1's predictive reach also extends to coagulation-related sequelae that frequently accompany septic AKI: Hatanaka and colleagues found that elevated circulating syndecan-1 predicted subsequent persistent thrombocytopenia and lethal outcome in patients with suspected sepsis requiring intensive care, implicating shared glycocalyx-mediated pathways linking renal and haemostatic dysfunction in this population [15].

Combining heparan sulphate-related biomarkers with other physiological or laboratory measures has consistently improved predictive performance beyond that achievable with any single marker. Zhang and colleagues reported that plasma syndecan-1 alone predicted sepsis-associated AKI with an AUC of 0.680, but that combining it with Doppler-measured renal resistive index, a marker of intrarenal vascular resistance, raised the AUC to 0.859 (sensitivity 87.8%, specificity 74.4%), with both markers retaining independent predictive value in multivariable analysis [16]. An even larger performance gain was reported by Salmito and colleagues, who found that combining syndecan-1 with angiopoietin-2 in a cohort of 127 critically ill patients already meeting KDIGO stage 2 AKI criteria improved discrimination for subsequent need for kidney support therapy within 72 hours from an AUC of 0.75 using clinical variables alone to 0.91 when the biomarker combination was added, with a continuous net reclassification improvement of 1.17 [17]. Across this literature, a consistent pattern emerges: circulating heparan sulphate and syndecan-1 carry genuine, independent predictive information for AKI and its downstream sequelae in sepsis, but their optimal clinical application appears to lie in combination with complementary haemodynamic, inflammatory, or established tubular injury markers rather than as a stand-alone test.

Fluid Resuscitation, Biomarker Kinetics, and Unresolved Questions

A central question for the clinical translation of heparan sulphate as an AKI biomarker in sepsis concerns whether its concentration is modifiable by resuscitation practice, and whether its prognostic value is independent of the treatment strategy chosen. This question has been most rigorously addressed within the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial, a multicentre, phase 3, randomised comparison of liberal fluid versus early vasopressor resuscitation strategies. In a secondary analysis of 574 CLOVERS participants, Oshima and colleagues found that higher baseline plasma heparan sulphate concentration was associated with a strikingly graded increase in mortality across tertiles, from 9.9% in the lowest tertile to 20.4% in the middle tertile and 44.2% in the highest tertile, with an adjusted hazard ratio of 3.12 per interquartile-range increase [18]. Notably, the randomised fluid strategy had no measurable effect on the degree of glycocalyx degradation at 24 hours, and baseline heparan sulphate concentration did not modify the treatment effect of the assigned resuscitation strategy, suggesting that the enzymatic and inflammatory drivers of glycocalyx shedding, rather than the volume or timing of resuscitation fluid, are the dominant determinants of heparan sulphate release in this population [18]. Fernández-Sarmiento, commenting on these findings, emphasised that plasma heparan sulphate demonstrated

stronger prognostic discrimination than several traditional clinical variables for 90-day outcomes, reinforcing the biomarker's potential clinical utility while noting that its independence from resuscitation strategy leaves open the question of what interventions, if any, might modify the trajectory of glycocalyx injury once it has begun [19].

A related analysis from the same investigator group examined plasma chondroitin sulphate, a related glycosaminoglycan released alongside heparan sulphate during glycocalyx degradation, and found that its concentration predicted both 90-day mortality and differential response to the randomised fluid resuscitation strategy in CLOVERS, raising the possibility that glycocalyx-derived glycosaminoglycan profiles could eventually be used not only to predict AKI and mortality risk but also to identify which patients are more or less likely to benefit from a liberal-fluid resuscitation approach [20]. This finding illustrates an important direction for the field: rather than treating heparan sulphate as an isolated univariate predictor, emerging work is beginning to characterise panels of glycosaminoglycan fragments whose combined kinetics may carry information relevant to both risk stratification and treatment selection.

Several limitations temper enthusiasm for immediate clinical adoption. Assay methodology remains heterogeneous, spanning immunoassays for shed syndecan-1 to mass-spectrometry-based quantification of heparan sulphate fragments, complicating cross-study comparison of absolute thresholds [9,13]. Most cohort studies to date have been single-centre and moderate in size, with the CLOVERS substudy a notable exception in scale and rigour [18]. Whether biomarker-guided intervention can improve outcomes rather than merely predict them remains untested and is the logical next step for this research programme.

Conclusion

The literature reviewed here converges on a coherent picture: circulating and urinary heparan sulphate, together with its principal clinical surrogate shed syndecan-1, constitute biologically plausible and empirically validated predictors of AKI in critically ill septic patients. This conclusion rests on a well-characterised anatomic and enzymatic foundation, in which the renal microvascular glycocalyx is degraded by heparanase and related sheddases during sepsis, releasing fragments into blood and urine that are detectable before conventional creatinine-based criteria register injury [3,4,6,10]. It is supported by a substantial epidemiological case, given that AKI complicates a majority of septic ICU admissions and carries independent mortality risk that scales with severity [8,2], and it is reinforced by a growing body of cohort studies demonstrating that heparan sulphate-related biomarkers, particularly when combined with renal resistive index, angiopoietin-2, or organ-dysfunction scores, achieve AUCs in the range of 0.77 to 0.91 for incident AKI or kidney support therapy [13,16,17,12]. Most persuasively, large trial-embedded analyses have shown a graded, dose-dependent association between baseline heparan sulphate concentration and mortality that is independent of randomised resuscitation strategy, indicating a robust and reproducible prognostic signal [18,20,19].

What remains unresolved is less the existence of this predictive relationship than its optimal clinical operationalisation: assay standardisation, prospective validation of specific cutoffs across diverse populations including paediatric sepsis [14], and, most importantly, interventional trials testing whether biomarker-guided management changes renal outcomes rather than merely forecasting them. As mass spectrometry and immunoassay platforms for glycosaminoglycan quantification become more widely accessible, circulating heparan sulphate is well positioned to move from a mechanistically compelling research biomarker toward a component of routine early risk stratification for AKI in septic critical illness.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Mihai Popescu conceived the review, conducted the literature search, and drafted the manuscript. Laurine Renaud contributed to the literature screening, extraction of quantitative findings from the primary studies, and critically revised the manuscript for important intellectual content. Signe Ozols contributed additional biochemical 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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