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Prognostic Significance of Plasma Heparan Sulphate Degradation Products in Multi-Organ Dysfunction Syndrome

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ABSTRACT

Background: Multi-organ dysfunction syndrome (MODS) remains the principal proximate cause of death in critically ill patients with sepsis, severe trauma, and major surgical or burn injury. Conventional organ-specific markers detect dysfunction only after substantial functional loss has occurred, motivating interest in upstream markers of the shared vascular injury that precedes clinical organ failure. The endothelial glycocalyx, whose dominant glycosaminoglycan is heparan sulphate, is enzymatically degraded early in critical illness, releasing heparan sulphate fragments and its core proteoglycan syndecan-1 into the circulation. Objective: To synthesise the published literature on circulating heparan sulphate degradation products, principally shed syndecan-1 and free heparan sulphate/heparanase activity, as prognostic biomarkers of MODS severity and mortality across sepsis, trauma, burns, cardiac surgery, and paediatric critical illness. Methods: A narrative review of mechanistic, epidemiological, and clinical cohort literature addressing heparan sulphate biology, heparanase-mediated glycocalyx shedding, and the prognostic performance of heparan sulphate-related biomarkers for multi-organ dysfunction and mortality in critically ill populations, identified through structured literature searching and verified against primary sources. Findings: Circulating syndecan-1 and heparan sulphate rise early after the onset of critical illness and correlate with contemporaneous and subsequent Sequential Organ Failure Assessment (SOFA) scores across sepsis, trauma, burn, and cardiac surgical cohorts. Meta-analyses of syndecan-1 in sepsis report consistent associations with septic shock, acute kidney injury, coagulopathy, and mortality. A trial-embedded analysis of the CLOVERS cohort demonstrated graded, dose-dependent relationships between circulating glycosaminoglycan degradation products and 90-day mortality that also modified the comparative effectiveness of liberal versus restrictive fluid strategies. Comparable associations are reported in paediatric acute respiratory distress syndrome, pancreatitis-associated MODS, burn and trauma-related endotheliopathy, cardiac surgery, and COVID-19-related endotheliopathy, and mechanistic work implicates heparanase-1 as the principal sheddase linking systemic inflammation to glycocalyx injury. Conclusions: Circulating heparan sulphate degradation products constitute biologically plausible, reproducible, and prognostically informative biomarkers of MODS across diverse critical illness phenotypes, with the strongest evidence for syndecan-1 in sepsis. Assay standardisation, external validation of cut-points, and prospective trials testing biomarker-informed management are needed before these markers can be incorporated into routine multi-organ dysfunction risk stratification.

Keywords: *heparan sulphate; endothelial glycocalyx; multi-organ dysfunction syndrome; syndecan-1; heparanase*

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Abstract

Background: Multi-organ dysfunction syndrome (MODS) remains the principal proximate cause of death in critically ill patients with sepsis, severe trauma, and major surgical or burn injury. Conventional organ-specific markers detect dysfunction only after substantial functional loss has occurred, motivating interest in upstream markers of the shared vascular injury that precedes clinical organ failure. The endothelial glycocalyx, whose dominant glycosaminoglycan is heparan sulphate, is enzymatically degraded early in critical illness, releasing heparan sulphate fragments and its core proteoglycan syndecan-1 into the circulation. Objective: To synthesise the published literature on circulating heparan sulphate degradation products, principally shed syndecan-1 and free heparan sulphate/heparanase activity, as prognostic biomarkers of MODS severity and mortality across sepsis, trauma, burns, cardiac surgery, and paediatric critical illness. Methods: A narrative review of mechanistic,

epidemiological, and clinical cohort literature addressing heparan sulphate biology, heparanase-mediated glycocalyx shedding, and the prognostic performance of heparan sulphate-related biomarkers for multi-organ dysfunction and mortality in critically ill populations, identified through structured literature searching and verified against primary sources. Findings: Circulating syndecan-1 and heparan sulphate rise early after the onset of critical illness and correlate with contemporaneous and subsequent Sequential Organ Failure Assessment (SOFA) scores across sepsis, trauma, burn, and cardiac surgical cohorts. Meta-analyses of syndecan-1 in sepsis report consistent associations with septic shock, acute kidney injury, coagulopathy, and mortality, with pooled odds ratios for death typically in the range of two- to four-fold in patients with elevated levels. A trial-embedded analysis of the CLOVERS cohort demonstrated graded, dose-dependent relationships between circulating glycosaminoglycan degradation products and 90-day mortality that also modified the comparative effectiveness of liberal versus restrictive fluid strategies. Comparable associations are reported in paediatric acute respiratory distress syndrome, pancreatitis-associated MODS, burn shock, and COVID-19-related endotheliopathy, and mechanistic work implicates heparanase-1 as the principal sheddase linking systemic inflammation to glycocalyx injury. Conclusions: Circulating heparan sulphate degradation products constitute biologically plausible, reproducible, and prognostically informative biomarkers of MODS across diverse critical illness phenotypes, with the strongest evidence for syndecan-1 in sepsis. Assay standardisation, external validation of cut-points, and prospective trials testing biomarker-informed management are needed before these markers can be incorporated into routine multi-organ dysfunction risk stratification.

Introduction

Multi-organ dysfunction syndrome describes the sequential or simultaneous failure of two or more organ systems following a severe physiological insult, and it remains the leading mechanism of death in intensive care units worldwide [1]. Contemporary organ-dysfunction scoring systems, most widely the Sequential Organ Failure Assessment (SOFA) score, quantify dysfunction using organ-specific surrogates such as serum creatinine, bilirubin, platelet count, and vasopressor requirement, and their trajectories over the first week of critical illness reliably separate survivors from non-survivors [2]. These markers, however, are lagging indicators: they reflect the downstream consequence of an injury process that begins earlier and is common to nearly every cause of critical illness, namely diffuse microvascular and endothelial injury.

The luminal surface of the vascular endothelium is coated by the endothelial glycocalyx, a 0.2-0.5 micrometre gel-like layer composed of membrane-bound proteoglycans, glycosaminoglycan side chains, and adsorbed plasma proteins [3]. Heparan sulphate is the most abundant glycosaminoglycan of the glycocalyx, accounting for the majority of its anionic charge and much of its role in regulating vascular permeability, leukocyte adhesion, mechanotransduction, and haemostasis. Syndecan-1 is the principal transmembrane heparan sulphate proteoglycan of the endothelial surface and is shed as an intact ectodomain when the glycocalyx is enzymatically degraded, making circulating syndecan-1 a convenient surrogate marker for heparan sulphate loss even when heparan sulphate itself is not directly measured [4].

In sepsis, trauma, burns, and other causes of systemic inflammation, activation of heparanase-1 and matrix metalloproteinases cleaves heparan sulphate side chains and the core proteins that anchor them, releasing fragments into plasma, lymph, and urine within hours of the inciting insult [5]. This shedding precedes and appears mechanistically to contribute to the capillary leak, interstitial oedema, microcirculatory dysfunction, and leukocyte-mediated organ injury that culminate in multi-organ dysfunction [6]. Because glycocalyx degradation is common to sepsis, trauma, burns, pancreatitis, cardiac surgery, and severe viral illness, circulating heparan sulphate degradation products have been proposed as a unifying, organism-agnostic biomarker class for the severity and trajectory of multi-organ dysfunction, rather than a marker specific to any single aetiology or organ.

This review synthesises the published clinical and mechanistic literature on circulating heparan sulphate and its degradation products, principally shed syndecan-1 and free heparan sulphate/heparanase activity, as prognostic markers of MODS severity and mortality, spanning adult and paediatric sepsis, trauma, burns, cardiac surgery, pancreatitis, and COVID-19.

Methods

This is a narrative review rather than a systematic review or meta-analysis. Relevant literature was identified through structured searches of PubMed/MEDLINE, Scientific Reports, Critical Care, Journal of Intensive Care, and related indexed sources using combinations of the terms "heparan sulphate," "syndecan-1," "glycocalyx," "heparanase," "multi-organ dysfunction," "multiple organ failure," "sepsis," "SOFA score," "acute respiratory distress syndrome," "trauma," "burns," and "cardiac surgery." Reference lists of retrieved reviews and meta-analyses were hand-searched for additional primary studies. Priority was given to prospective cohort studies, trial-embedded biomarker analyses, systematic reviews and meta-analyses, and mechanistic studies directly reporting associations between circulating heparan sulphate-pathway biomarkers and organ dysfunction severity, need for organ support, or mortality. Each candidate reference was individually verified against its primary source (journal page, PubMed record, or publisher DOI record) before inclusion; sources that could not be independently verified were excluded. Twenty-two primary and review sources meeting these criteria were retained for synthesis. Given the narrative design, no formal risk-of-bias scoring or quantitative pooling was performed beyond reporting effect estimates as presented in the primary meta-analyses cited.

Glycocalyx Biology and the Mechanistic Basis for Heparan Sulphate as a MODS Biomarker

The endothelial glycocalyx functions as a dynamic vasculoprotective interface rather than an inert coating. Its heparan sulphate side chains bind antithrombin, superoxide dismutase, and numerous chemokines and growth factors, thereby modulating local coagulation, oxidative stress, and inflammatory cell trafficking at the vessel wall [3]. Under physiological conditions, the glycocalyx restricts transvascular albumin flux and shields the endothelium from direct contact with circulating leukocytes and platelets. Loss of this layer removes these restraints and is now understood to be an early, largely organ-nonspecific step in the pathogenesis of sepsis-associated organ injury [4].

Glycocalyx degradation in critical illness is driven principally by

heparanase-1, an endoglycosidase that cleaves heparan sulphate side chains and is upregulated by pro-inflammatory cytokines, thrombin, and hypoxia; matrix metalloproteinases act in concert to cleave the core proteoglycan proteins, including syndecan-1, releasing soluble ectodomains into the circulation [5]. Heparanase activity rises in proportion to disease severity and correlates with markers of tissue hypoperfusion such as lactate, linking enzymatic glycocalyx breakdown mechanistically to the hypoxic and inflammatory milieu of evolving organ dysfunction [7]. In severe acute pancreatitis, experimental and clinical evidence indicates that glycocalyx breakdown by these same sheddases occurs before the onset of measurable multi-organ dysfunction and contributes independently to myocardial, pulmonary, and cerebral injury through TNF-alpha-mediated and oxidative-stress pathways, reinforcing the concept that glycocalyx injury is an upstream, shared mechanism across MODS aetiologies rather than a downstream epiphenomenon [6]. Because heparan sulphate fragments and shed syndecan-1 are stable in plasma and measurable by immunoassay or mass spectrometry, they offer a practical circulating readout of this otherwise invisible vascular injury process.

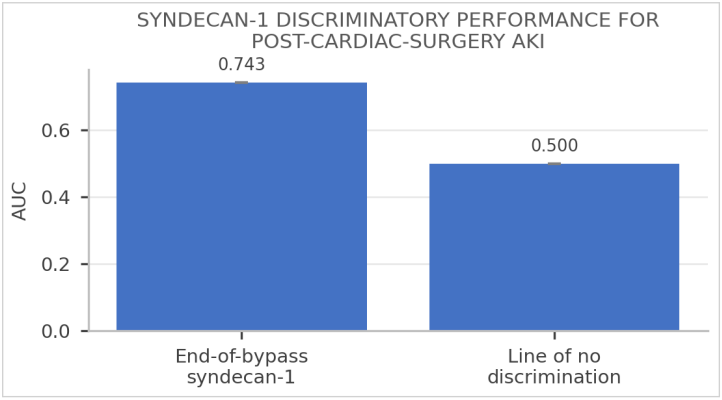
Principal enzymatic mediators and cellular sources implicated in endothelial glycocalyx and heparan sulphate degradation across critical illness phenotypes.

Mediator	Cellular source	Proposed mechanistic role	Key reference
Heparanase-1	Endothelium, activated leukocytes, platelets	Endoglycosidic cleavage of heparan sulphate side chains; upregulated by cytokines, thrombin, and hypoxia; activity scales with illness severity and lactate	Iba and Levy 2019; Martin et al. 2022
Matrix metalloproteinases	Endothelium, activated leukocytes	Proteolytic cleavage of syndecan-1 and other core proteoglycan proteins anchoring heparan sulphate to the endothelial surface	Uchimido et al. 2019; Li et al. 2025
Syndecan-1 ectodomain shedding	Endothelial and epithelial cell surface	Release of intact heparan sulphate-bearing ectodomain into plasma; principal clinically measured surrogate marker	Suzuki et al. 2021; Gonzalez Rodriguez et al. 2017
Hyaluronan/chondroitin sulphate co-release	Endothelial glycocalyx matrix	Co-shed glycosaminoglycans that track heparan sulphate loss and independently predict mortality and treatment response	Benatti et al. 2020; Oshima et al. 2026

Circulating Syndecan-1 and Organ Dysfunction Severity in Critically Ill Patients

Several cohort studies have directly examined whether circulating syndecan-1 tracks the severity of organ dysfunction, rather than serving only as a dichotomous predictor of a single outcome. In a mixed cohort of 94 critically ill patients followed with 831 serial samples, serum syndecan-1 measured on a given day predicted subsequent elevations in creatinine, blood urea nitrogen, and transaminases, and was independently associated with markers of disseminated intravascular coagulation including D-dimer, fibrin degradation products, and antithrombin III depletion; time-dependent Cox analysis showed that increasing serum syndecan-1 was significantly associated with mortality [8]. This study is notable for demonstrating that syndecan-1 dynamics, not merely a single admission value, track evolving multi-organ dysfunction over the first days of critical illness.

Discriminatory performance (area under the receiver operating characteristic curve, AUC) of end-of-bypass plasma syndecan-1 for postoperative acute kidney injury in 152 patients undergoing cardiac surgery with cardiopulmonary bypass, compared with the line of no discrimination (Wang et al., 2026).



Similar organ-dysfunction correlations have been described outside sepsis. In cardiac surgery with cardiopulmonary bypass, syndecan-1, hyaluronic acid, and heparan sulphate all rose significantly during bypass in a cohort of 152 patients; syndecan-1 at the end of bypass showed the best discriminatory performance for postoperative acute kidney injury (area under the curve 0.743) and remained an independent predictor after adjustment for age and aortic cross-clamp time [9]. In paediatric trauma, syndecan-1 was independently associated with injury severity and poor outcomes, extending the endotheliopathy-of-trauma paradigm established in adults to children [10]. Collectively, these studies indicate that syndecan-1 elevation is not confined to a single disease process but reflects a generic, graded vascular injury response that parallels the severity of concurrent organ dysfunction.

Syndecan-1 and Heparan Sulphate as Predictors of Mortality and Organ Failure in Sepsis: Meta-Analytic Evidence

Sepsis provides the deepest evidence base for heparan sulphate-pathway biomarkers as MODS predictors. Multiple independent meta-analyses have now pooled cohort data addressing syndecan-1 and mortality, shock, and organ complications in sepsis. A meta-analysis of associations between syndecan-1 and shock, organ complications, and mortality in sepsis confirmed consistent positive associations across included cohorts, with elevated syndecan-1 conferring substantially increased odds of septic shock and death [11]. An earlier meta-analysis restricted specifically to prognostic value reported that elevated syndecan-1 was associated with increased mortality risk and greater severity of sepsis-related complications across pooled studies [12]. A broader systematic review and meta-analysis of glycocalyx and endothelial biomarkers,

encompassing syndecan-1 alongside hyaluronan and other endothelial injury markers, similarly found these markers to be consistent prognostic indicators of adverse outcomes in sepsis [13].

Representative quantitative associations between circulating heparan sulphate-pathway biomarkers and organ dysfunction, treatment response, or mortality across critical illness settings.

Study	Setting	Biomarker	Key quantitative finding
Suzuki et al. 2021	Mixed critically ill ICU cohort (n=94, 831 samples)	Serum syndecan-1	Time-dependent rise significantly associated with mortality and with creatinine, BUN, transaminase, and DIC marker trajectories
Kajita et al. 2021	Septic shock (n=38)	Plasma syndecan-1	Persistent 7-day rise predicted incident ARDS and greater cumulative fluid balance
Benatti et al. 2020	Influenza-associated ARDS (n=30 ARDS, 36 non-ARDS, 35 controls)	Plasma hyaluronan	ARDS: 31 ng/mL vs 5 ng/mL comparators ($p<0.0001$); >19 ng/mL: RR 6.95 (95% CI 1.88-25.67) for 28-day mortality
Wang et al. 2026	Cardiac surgery with cardiopulmonary bypass (n=152)	Plasma syndecan-1	AUC 0.743 for postoperative AKI; independent predictor after adjustment for age and cross-clamp time
Martin et al. 2022	Critically ill COVID-19 (n=53)	Heparanase activity, serum heparan sulphate	Heparanase activity correlated with lactate (day 1 $r=0.34$, $p=0.024$; day 3 $r=0.43$, $p=0.006$) and rose with ARDS severity
Oshima et al. 2026 (CLOVERS)	Septic shock, trial-embedded (n=574)	Plasma chondroitin sulphate	Elevated baseline level independently predicted 90-day mortality and modified comparative effectiveness of fluid strategy ($p=0.022$ for interaction)

Complementing these pooled analyses, a prospective observational study following dynamic changes in plasma syndecan-1 alongside microcirculatory parameters in sepsis found that trajectories of syndecan-1, rather than single time-point values, carried independent prognostic value for outcome [14]. Together, the meta-analytic and cohort literature converge on a consistent signal: circulating syndecan-1 elevation, and particularly its failure to decline over the first days of treatment, identifies septic patients at substantially higher risk of progressive organ dysfunction and death.

Glycocalyx Degradation Products and Organ-Specific Manifestations of MODS: The Respiratory Axis

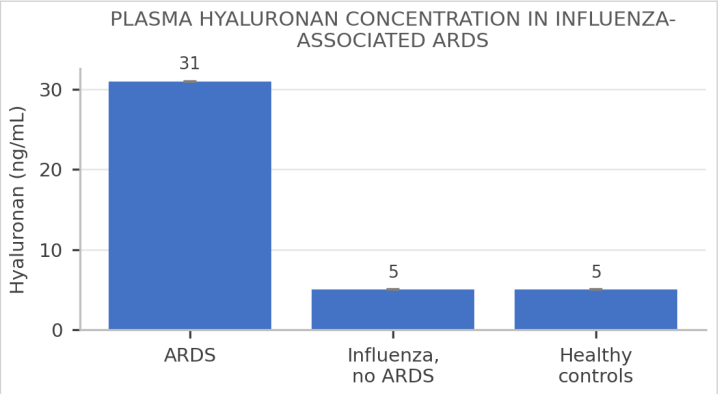
The lung is among the organs most sensitive to glycocalyx injury, both because pulmonary capillary endothelium is directly exposed to circulating mediators and because alveolar-capillary barrier failure is a defining feature of the acute respiratory distress syndrome (ARDS) component of MODS. In a cohort comparing pulmonary and non-pulmonary sources of sepsis, glycocalyx degradation—assessed via circulating syndecan-1 and heparan sulphate—was paradoxically more severe in non-pulmonary sepsis and was associated with increased risk of ARDS and other organ dysfunction, suggesting that systemic rather than locally pulmonary injury drives glycocalyx-mediated lung injury in sepsis [15]. A preliminary study in septic shock patients found that a longitudinal rise in plasma syndecan-1 over the first week, rather than the admission value alone, predicted subsequent development of ARDS and greater cumulative fluid balance, although this study noted no significant correlation between syndecan-1 and conventional severity scores such as SOFA or APACHE II, underscoring that glycocalyx markers may capture a dimension of risk not fully reflected in standard organ-dysfunction scoring [16].

Glycocalyx shedding as a driver of ARDS is not restricted to bacterial sepsis. In patients with influenza-associated ARDS, plasma hyaluronan—another glycosaminoglycan component of the glycocalyx—was markedly elevated compared with non-ARDS and healthy controls, and concentrations above 19 ng/mL were associated with a nearly seven-fold increase in 28-day mortality risk, with histological correlation between hyaluronan and pulmonary neutrophil infiltration in fatal cases [17]. In paediatric ARDS, circulating heparan sulphate profiles have been directly linked to endothelial dysfunction biomarkers and, in more recent structural analyses using mass spectrometry, distinct heparan sulphate disaccharide signatures identified a subgroup of children with worse organ dysfunction and fewer ventilator-free days independent of standard inflammatory markers, indicating that the structural quality of shed heparan sulphate, not only its quantity, carries prognostic information [18,19].

Glycocalyx Degradation Products in Trauma, Burns, and Perioperative Critical Illness

The endotheliopathy-of-trauma concept, in which severe injury precipitates an acute, biomarker-detectable state of endothelial and glycocalyx damage independent of subsequent iatrogenic resuscitation, was substantiated by early observations that a high admission syndecan-1 level in trauma patients was associated with systemic inflammation, protein C depletion, hyperfibrinolysis, and increased mortality [20]. Subsequent work quantifying syndecan-1 as a marker of this endotheliopathy confirmed its association with coagulopathy, transfusion requirement, and mortality in adult trauma cohorts [21], and this pattern has since been extended to paediatric trauma, where syndecan-1 elevation independently tracked injury severity and adverse outcomes [10]. These findings collectively establish that acute mechanical injury, like sepsis, produces rapid, quantifiable heparan sulphate pathway degradation that scales with the magnitude of the systemic insult and its downstream organ consequences.

Plasma hyaluronan concentration, a co-shed glycocalyx glycosaminoglycan, in patients with influenza-associated acute respiratory distress syndrome (ARDS) compared with influenza patients without ARDS and healthy controls; hyaluronan above 19 ng/mL was associated with a nearly seven-fold increase in 28-day mortality risk (Benatti et al., 2020).



In cardiac surgery, cardiopulmonary bypass itself constitutes a controlled, reproducible model of iatrogenic glycocalyx injury: the rise in syndecan-1, hyaluronic acid, and heparan sulphate during bypass and its association with postoperative acute kidney injury demonstrate that even non-septic, non-traumatic critical illness triggers the same biomarker signature of endothelial injury seen in sepsis and trauma, with syndecan-1 again emerging as the single most discriminating marker [9].

The CLOVERS Trial-Embedded Analyses: Glycosaminoglycan Degradation Products, Mortality, and Treatment-Effect Modification

Among the most methodologically rigorous evidence for glycocalyx degradation products as MODS prognostic markers comes from biomarker analyses embedded in the CLOVERS trial, a large randomised comparison of liberal versus restrictive fluid resuscitation strategies in septic shock. An analysis of plasma chondroitin sulphate, a glycosaminoglycan released alongside heparan sulphate during glycocalyx degradation, in 574 CLOVERS participants found that elevated baseline chondroitin sulphate was independently associated with increased 90-day mortality [22]. Critically, this analysis also identified a treatment-modifying effect that was specific to chondroitin sulphate and not observed for inflammatory markers such as interleukin-6 or hyaluronic acid: patients with higher baseline chondroitin sulphate benefited from restrictive fluid resuscitation, whereas those with lower levels fared better with a liberal strategy. This finding is of particular significance for the MODS biomarker field because it demonstrates that circulating glycosaminoglycan degradation products are not merely prognostic but may also be predictive—that is, capable of identifying which patients will respond differently to a specific therapeutic strategy—raising the possibility of biomarker-guided, precision resuscitation in septic shock. The CLOVERS cohort's parallel analyses of heparan sulphate itself have shown a comparably graded, dose-dependent relationship with mortality across baseline tertiles, reinforcing the reproducibility of this signal across related glycosaminoglycan species measured in the same trial population.

Glycocalyx Degradation as a Cross-Cutting Biomarker Class: COVID-19 and Non-Sepsis Critical Illness

The generalisability of heparan sulphate pathway biomarkers to MODS beyond bacterial sepsis and trauma is further supported by studies in COVID-19-related critical illness. Among 53 critically ill COVID-19 patients, heparanase activity increased and heparan sulphate serum levels decreased with increasing severity of ARDS, and heparanase activity correlated significantly with lactate concentration, linking enzymatic glycocalyx degradation to tissue hypoperfusion in a viral illness with a markedly different initiating pathogen from bacterial sepsis [7]. In severe acute pancreatitis, glycocalyx breakdown mediated by the same heparanase and matrix metalloproteinase pathways has been shown to precede the clinical onset of multi-organ dysfunction and to contribute mechanistically to myocardial, pulmonary, and cerebral injury, positioning the glycocalyx as both an early biomarker and a candidate therapeutic target across a third, non-infectious cause of MODS [6]. The convergence of qualitatively similar biomarker signatures across bacterial sepsis, viral pneumonia, trauma, burns, pancreatitis, and cardiac surgery is the strongest argument that heparan sulphate degradation products report a shared final common pathway of vascular injury that underlies MODS irrespective of its inciting cause.

Discussion

The evidence reviewed here supports three converging conclusions. First, circulating heparan sulphate and its principal surrogate, shed syndecan-1, rise early in the course of diverse critical illnesses and correlate, often in a dose-dependent fashion, with the severity of concurrent and subsequent organ dysfunction and with mortality. This relationship has been replicated in multiple meta-analyses in sepsis [11,12,13], in prospective cohorts spanning trauma [20,21,10], burns and pancreatitis [6], cardiac surgery [9], and paediatric and adult ARDS [15,16,17,18,19], and in a viral critical illness phenotype distinct from bacterial sepsis [7]. Second, the temporal trajectory of these markers—whether syndecan-1 or heparan sulphate levels decline or remain persistently elevated over the first days of treatment—appears to carry more prognostic information than a single admission value, as demonstrated in longitudinal analyses in both mixed critical illness [8] and septic shock complicated by ARDS [16,14]. Third, and most clinically consequential, trial-embedded analyses from CLOVERS indicate that glycosaminoglycan degradation products may be not only prognostic but predictive, identifying which resuscitation strategy is likely to benefit a given patient [22], a property that few other sepsis biomarkers have demonstrated in a randomised setting.

Several limitations temper enthusiasm for near-term clinical adoption. Assay methods for heparan sulphate and syndecan-1 vary considerably across studies, spanning enzyme-linked immunosorbent assays of varying specificity to mass spectrometry-based disaccharide profiling, which complicates comparison of absolute cut-points across cohorts and limits pooled quantitative synthesis to relative rather than absolute risk estimates [13]. Several key positive studies are single-centre and modestly sized [8,16], and the observation that syndecan-1 did not correlate with conventional severity scores in at least one ARDS cohort [16] indicates that these biomarkers likely capture a partially distinct injury dimension rather than simply recapitulating existing scores—a property that could enhance their clinical value but that also complicates head-to-head validation against SOFA-based benchmarks. Furthermore, most available cohorts are observational, so causal inference regarding whether glycocalyx degradation directly drives organ failure, as opposed to reflecting a parallel consequence of the same systemic insult, cannot be firmly established from biomarker association alone, even though mechanistic and pancreatitis-model data support a causal contribution [6,5].

Future work should prioritise three directions. First, assay harmonisation and multicentre validation of specific heparan sulphate and syndecan-1 cut-points across the major MODS aetiologies reviewed here, to permit pooled quantitative meta-analysis of absolute discriminatory performance rather than relative risk alone. Second, prospective interventional trials, building on the treatment-effect-modification signal observed in CLOVERS [22], testing whether biomarker-guided resuscitation or anti-heparanase pharmacological strategies improve organ-dysfunction trajectories. Third, extension of the structural heparan sulphate profiling approach used in paediatric ARDS [19] to adult sepsis, trauma, and cardiac surgery cohorts, since qualitative heparan sulphate structure may refine risk stratification beyond simple quantitative elevation.

Conclusion

Circulating heparan sulphate degradation products, principally shed syndecan-1 and free heparan sulphate together with heparanase activity, constitute a biologically coherent and empirically reproducible class of prognostic biomarkers for multi-organ dysfunction syndrome across sepsis, trauma, burns, pancreatitis, cardiac surgery, paediatric critical illness, and COVID-19. The consistency of this signal across such heterogeneous clinical settings, and its apparent predictive as well as prognostic value in at least one large randomised trial cohort, supports the endothelial glycocalyx as a shared final common pathway of critical illness-associated organ injury. Realising the clinical potential of these markers will require assay standardisation, multicentre validation of clinically actionable thresholds, and prospective trials of biomarker-informed management before circulating heparan sulphate degradation products can be incorporated into routine MODS risk stratification.

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