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ENDOTHELIAL INJURY MARKERS AS PROGNOSTIC PREDICTORS IN CRITICALLY ILL PATIENTS: A REVIEW OF RECENT CLINICAL EVIDENCE

MARCADORES DE LESÃO ENDOTELIAL COMO PREDITORES PROGNÓSTICOS EM PACIENTES CRITICAMENTE ENFERMOS: UMA REVISÃO DAS EVIDÊNCIAS CLÍNICAS RECENTES

MARCADORES DE LESIÓN ENDOTELIAL COMO PREDICTORES PRONÓSTICOS EN PACIENTES CRÍTICAMENTE ENFERMOS: UNA REVISIÓN DE LA EVIDENCIA CLÍNICA RECIENTE

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ABSTRACT

Introduction: Sepsis and septic shock remain associated with high mortality in intensive care, and endothelial dysfunction plays a central role in the pathophysiology of organ failure. Biomarkers of endothelial injury have been investigated as tools for prognostic stratification and early identification of high-risk patients. However, methodological heterogeneity and the lack of standardized cutoff values hinder their routine clinical application.

Objective: To systematically and critically evaluate the association between biomarkers of endothelial dysfunction and mortality in adult patients with sepsis or septic shock, based on recent clinical evidence published over the last five years. Secondary objectives were to identify the biomarkers most consistently associated with mortality, compare their prognostic performance with the Sequential Organ Failure Assessment and lactate, analyze the impact of single versus serial measurement, explore sources of methodological heterogeneity, and estimate certainty of evidence using standardized instruments.

Methods: A search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP, without language restriction, prioritizing human studies published within the last five years. Clinical studies in adults with sepsis or septic shock that measured at least one endothelial biomarker and reported its association with mortality were included. Risk of bias was assessed using RoB 2, ROBINS-I, and QUADAS-2 according to study design, and certainty of evidence was estimated using GRADE, with predominantly qualitative synthesis and meta-analysis only when sufficient homogeneity was present.

Results and Discussion: Twenty studies were included in the qualitative synthesis. Syndecan-1 and angiopoietin-2 were the biomarkers most frequently associated with higher mortality and greater severity, whereas endocan and soluble thrombomodulin showed variable performance, influenced by timing of collection and clinical context. Studies using serial measurements suggested a potential advantage of temporal trajectories for risk

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discrimination, but comparability was limited by heterogeneity in clinical definitions, analytical platforms, and outcomes. Certainty of evidence ranged from low to moderate, mainly because of the predominance of observational studies, risk of confounding, and inconsistency across studies.

Conclusion: Biomarkers of endothelial injury, especially syndecan-1 and angiopoietin-2, are consistently associated with worse prognosis in sepsis and septic shock and may complement clinical scores and lactate in risk stratification. Broad clinical implementation still depends on analytical standardization, definition of cutoff values, and external validation, in addition to pragmatic studies demonstrating incremental clinical benefit in biomarker-guided algorithms.

Keywords: Sepsis. Septic Shock. Endothelium. Biomarkers.

RESUMO

Introdução: A sepse e o choque séptico permanecem associados a alta mortalidade em unidades de terapia intensiva, e a disfunção endotelial desempenha um papel central na fisiopatologia da falência de órgãos. Biomarcadores de lesão endotelial têm sido investigados como ferramentas para estratificação prognóstica e identificação precoce de pacientes de alto risco. No entanto, a heterogeneidade metodológica e a ausência de valores de corte padronizados dificultam sua aplicação clínica rotineira.

Objetivo: Avaliar de forma sistemática e crítica a associação entre biomarcadores de disfunção endotelial e mortalidade em pacientes adultos com sepse ou choque séptico, com base em evidências clínicas recentes publicadas nos últimos cinco anos. Os objetivos secundários foram identificar os biomarcadores mais consistentemente associados à mortalidade, comparar seu desempenho prognóstico com o Sequential Organ Failure Assessment e o lactato, analisar o impacto de medições únicas versus seriadas, explorar fontes de heterogeneidade metodológica e estimar a certeza da evidência utilizando instrumentos padronizados.

Métodos: Foi realizada uma busca nas bases de dados PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP, sem restrição de idioma, priorizando estudos em humanos publicados nos últimos cinco anos. Foram incluídos estudos clínicos em adultos com sepse ou choque séptico que mediram pelo menos um biomarcador endotelial e relataram sua associação com mortalidade. O risco de viés foi avaliado utilizando RoB 2, ROBINS-I e QUADAS-2 de acordo com o delineamento do estudo, e a certeza da evidência foi estimada pelo GRADE, com síntese predominantemente qualitativa e metanálise apenas quando havia homogeneidade suficiente.

Resultados e Discussão: Vinte estudos foram incluídos na síntese qualitativa. Syndecan-1 e angiopoietina-2 foram os biomarcadores mais frequentemente associados a maior mortalidade e maior gravidade, enquanto endocan e trombomodulina solúvel apresentaram desempenho variável, influenciado pelo momento da coleta e pelo contexto clínico. Estudos que utilizaram medições seriadas sugeriram uma possível vantagem das trajetórias temporais para discriminação de risco, porém a comparabilidade foi limitada pela heterogeneidade nas definições clínicas, plataformas analíticas e desfechos avaliados. A certeza da evidência variou de baixa a moderada, principalmente devido à predominância de estudos observacionais, risco de confundimento e inconsistência entre os estudos.

Conclusão: Biomarcadores de lesão endotelial, especialmente syndecan-1 e angiopoietina-2, estão consistentemente associados a pior prognóstico na sepse e no choque séptico e podem complementar escores clínicos e níveis de lactato na estratificação de risco. A

implementação clínica ampla ainda depende da padronização analítica, da definição de valores de corte e da validação externa, além de estudos pragmáticos que demonstrem benefício clínico incremental em algoritmos guiados por biomarcadores.

Palavras-chave: Sepse. Choque Séptico. Endotélio. Biomarcadores.

RESUMEN

Introducción: La sepsis y el shock séptico continúan asociados con una alta mortalidad en las unidades de cuidados intensivos, y la disfunción endotelial desempeña un papel central en la fisiopatología de la falla orgánica. Los biomarcadores de lesión endotelial han sido investigados como herramientas para la estratificación pronóstica y la identificación temprana de pacientes de alto riesgo. Sin embargo, la heterogeneidad metodológica y la falta de valores de corte estandarizados dificultan su aplicación clínica rutinaria.

Objetivo: Evaluar de forma sistemática y crítica la asociación entre biomarcadores de disfunción endotelial y mortalidad en pacientes adultos con sepsis o shock séptico, con base en evidencia clínica reciente publicada en los últimos cinco años. Los objetivos secundarios fueron identificar los biomarcadores más consistentemente asociados con la mortalidad, comparar su desempeño pronóstico con el Sequential Organ Failure Assessment y el lactato, analizar el impacto de mediciones únicas frente a mediciones seriadas, explorar fuentes de heterogeneidad metodológica y estimar la certeza de la evidencia utilizando instrumentos estandarizados.

Métodos: Se realizó una búsqueda en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP, sin restricción de idioma, priorizando estudios en humanos publicados en los últimos cinco años. Se incluyeron estudios clínicos en adultos con sepsis o shock séptico que midieron al menos un biomarcador endotelial y reportaron su asociación con la mortalidad. El riesgo de sesgo fue evaluado utilizando RoB 2, ROBINS-I y QUADAS-2 según el diseño del estudio, y la certeza de la evidencia fue estimada mediante GRADE, con síntesis predominantemente cualitativa y metaanálisis solo cuando existía suficiente homogeneidad.

Resultados y Discusión: Veinte estudios fueron incluidos en la síntesis cualitativa. Syndecan-1 y angiopoyetina-2 fueron los biomarcadores más frecuentemente asociados con mayor mortalidad y mayor gravedad, mientras que endocan y trombomodulina soluble mostraron un desempeño variable, influenciado por el momento de la recolección y el contexto clínico. Los estudios que utilizaron mediciones seriadas sugirieron una posible ventaja de las trayectorias temporales para la discriminación del riesgo, aunque la comparabilidad fue limitada por la heterogeneidad en las definiciones clínicas, las plataformas analíticas y los resultados evaluados. La certeza de la evidencia varió de baja a moderada, principalmente debido al predominio de estudios observacionales, al riesgo de confusión y a la inconsistencia entre los estudios.

Conclusión: Los biomarcadores de lesión endotelial, especialmente syndecan-1 y angiopoyetina-2, están consistentemente asociados con peor pronóstico en la sepsis y el shock séptico y pueden complementar las escalas clínicas y los niveles de lactato en la estratificación del riesgo. La implementación clínica amplia aún depende de la estandarización analítica, la definición de valores de corte y la validación externa, además de estudios pragmáticos que demuestren un beneficio clínico incremental en algoritmos guiados por biomarcadores.

Palabras clave: Sepsis. Shock Séptico. Endotelio. Biomarcadores.

1 INTRODUCTION

Mortality in intensive care units remains high despite advances in hemodynamic, ventilatory, and antimicrobial support, reinforcing the need for better prognostic stratification tools in daily practice.[1] Sepsis and septic shock continue to be central clinical models of critical illness because they combine circulatory instability, systemic inflammation, and multiple organ failure within a short time interval.[1] Recent international guidelines emphasize that early recognition of patients at greater risk, followed by timely interventions proportionate to severity, is decisive for outcomes.[1] Based on this rationale, interest in biomarkers that capture the biology of critical illness more directly than isolated clinical scores has been expanding rapidly.[2]

Among the pathophysiological axes connecting different critical syndromes, endothelial dysfunction occupies a prominent position because it integrates alterations in permeability, microcirculation, hemostasis, and inflammation.[2] Contemporary reviews describe that endothelial glycocalyx injury, leukocyte activation, and loss of integrity of intercellular junctions may amplify capillary leakage and perpetuate tissue hypoperfusion.[2] In this context, circulating markers reflecting glycocalyx degradation and endothelial activation have been proposed as measurable “signatures” of biological severity.[2] The clinical relevance of this paradigm also appears in reviews focused on “glycocalyx-friendly” therapeutic strategies, suggesting that measuring endothelial injury may provide additional value beyond syndromic diagnosis.[3]

Angiopoietin-2 (Angiopoietin-2, Ang-2) has been highlighted as a marker of endothelial activation and vascular destabilization, with biological plausibility for association with shock, acute respiratory distress syndrome, and mortality.[3] A recent meta-analysis in adults with sepsis synthesized evidence showing that higher Ang-2 levels correlate with worse prognosis and greater risk of death.[3] Contemporary clinical studies have also observed prognostic value for Ang-2 measured early in critically ill patients with sepsis, reinforcing consistency across different care settings.[3] Even so, variations in timing of collection, analytical platforms, and cutoff values still limit direct comparability between centers and studies.[4]

Damage to the endothelial glycocalyx can be operationalized through biomarkers such as syndecan-1 (Syndecan-1, SDC-1), which increases when proteoglycan shedding occurs from the endothelial surface.[4] A meta-analysis specifically devoted to SDC-1 concluded that elevated baseline concentrations are associated with higher risk of sepsis-related complications and mortality, suggesting potential utility for early stratification.[4] A broader synthesis, including markers of glycocalyx injury and endothelial activation, also found a consistent association between elevation of these biomarkers and adverse clinical outcomes,

although with heterogeneity among studies.[4] Nevertheless, uncertainties remain regarding how to integrate SDC-1 into real-time therapeutic decisions, especially in scenarios of marked clinical variability and simultaneous interventions.[5]

In addition to glycocalyx markers, biomarkers linked to endothelial adhesion and activation, such as intercellular and vascular adhesion molecules, have been evaluated as indicators of microvascular dysfunction and endothelial inflammation.[5] A recent systematic review and meta-analysis showed that elevated plasma levels of ICAM1 (Intercellular Adhesion Molecule-1, ICAM-1) and VCAM1 (Vascular Cell Adhesion Molecule-1, VCAM-1) are associated with sepsis, septic shock, multiple organ dysfunction, and mortality, supporting their utility as severity biomarkers.[5] These results suggest that signals of endothelial activation may capture prognostic risk through pathways distinct from those measured by lactate or organ dysfunction scores.[5] However, reliance on observational studies and the possibility of confounding by baseline severity require cautious interpretation when extrapolating toward causality.[6]

Within the spectrum of endothelial injury, soluble thrombomodulin (Soluble Thrombomodulin, sTM) reflects endothelial surface damage and dysregulation of endogenous anticoagulation and has been proposed as a risk marker in sepsis and septic shock.[6] Recent studies have evaluated sTM in septic populations, focusing on mortality prediction and correlation with organ dysfunction, supporting its plausibility for prognostic use.[6] In this setting, endothelial injury is also connected to the phenotype of sepsis-associated coagulopathy, a topic addressed in contemporary reviews discussing traditional and emerging markers for risk stratification.[6] Although promising, the clinical use of sTM still faces barriers related to assay standardization, availability, and definition of reproducible thresholds across centers.[7]

Another relevant pathway involves bioactive adrenomedullin (Bioactive Adrenomedullin, bio-ADM), which is related to vasoplegia and control of vascular permeability, with potential to indicate support requirements and risk of unfavorable outcomes.[7] In a recent emergency department study, bio-ADM was associated with mortality, organ failure, and need for intensive care admission, suggesting a role in triage and escalation of care.[7] This type of evidence reinforces the idea that endothelial biomarkers may serve as a bridge between pathophysiology and early care decisions in critically ill patients.[7] Still, extrapolation to different etiologies of critical illness and to settings with distinct resuscitation protocols remains a gap.[8]

Despite the growing volume of publications, the field suffers from methodological heterogeneity, including variable clinical definitions, different timing of collection, and

differences in concomitant treatment that may modify biomarkers and outcomes.[8] Recent reviews of biomarkers in sepsis emphasize that multimarker strategies and integrated approaches tend to outperform a single isolated biomarker, but they still lack robust external validation.[8] In parallel, reviews focused on endothelial dysfunction reinforce that endothelial injury is a transversal component of multiple critical syndromes, which may be an advantage for generalization but also a risk for loss of diagnostic specificity.[8] These conceptual tensions make a systematic synthesis necessary, one that prioritizes consistency of association with prognosis and methodological quality while also mapping implementation limitations.[9]

In view of this scenario, it becomes essential to critically organize recent evidence on markers of endothelial injury as predictors of prognosis in critically ill patients, focusing on mortality and clinically relevant outcomes.[9] The integration of biomarkers of endothelial activation, glycocalyx degradation, and coagulopathy may offer a more pathophysiological framework for risk stratification than exclusively clinical models.[9] Moreover, reviews directed at “glycocalyx-friendly” management indicate that the interpretation of endothelial biomarkers may interact with therapeutic choices, although this translation remains incomplete.[9] Thus, this systematic review was designed to synthesize recent clinical evidence, identify markers with the most consistent association with prognosis, and highlight priority gaps for research and implementation in intensive care.[10]

2 OBJECTIVES

2.1 GENERAL OBJECTIVE

To systematically and critically evaluate the association between biomarkers of endothelial dysfunction and mortality in adult patients with sepsis or septic shock, based on recent clinical evidence published over the last five years.

2.2 SPECIFIC OBJECTIVES

To identify which biomarkers of endothelial dysfunction show a statistically significant association with short-term mortality, especially at 28 days or during hospital stay.

To compare the prognostic performance of these biomarkers with established clinical scores, such as the Sequential Organ Failure Assessment (SOFA), and with widely used laboratory markers such as serum lactate.

To analyze whether single or serial biomarker measurement influences their predictive capacity for fatal outcomes.

To assess methodological heterogeneity among the included studies, considering differences in design, population, timing of collection, and laboratory techniques used.

3 METHODOLOGY

This systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), with prior definition of the question, eligibility criteria, outcomes, and synthesis plan. The research question evaluated, in adults with sepsis or septic shock, the association between biomarkers of endothelial dysfunction or injury and mortality. The primary outcome was short-term mortality, especially at 28 days, in the intensive care unit, or during hospital stay, as reported in the studies, and secondary outcomes included organ dysfunction (Sequential Organ Failure Assessment, SOFA), need for vasopressors and mechanical ventilation, and length of stay in intensive care and in hospital.

The search was performed in PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP), using descriptors and keywords related to sepsis, septic shock, endothelium, and biomarkers, without language restriction. The main inclusion period was five years, with expansion to ten years if fewer than ten eligible studies were found. Human studies were prioritized; experimental data, when relevant, were planned for separate presentation.

Clinical studies in adults with sepsis or septic shock that measured at least one endothelial biomarker and analyzed its association with mortality were included. Clinical trials and observational studies (prospective or retrospective) were eligible, whereas case reports, exclusively pediatric studies, and articles without sufficient data for extraction were excluded. Selection occurred in two stages (titles/abstracts and full text), with independent reviewers, duplicate removal, and resolution of disagreements by consensus. Data extraction included study design, population, biomarkers (method and timing of collection), measures of association, and adjustments for confounders.

Risk of bias was assessed using RoB 2 for randomized trials, ROBINS-I for non-randomized studies, and QUADAS-2 when applicable. Certainty of evidence was estimated using GRADE. Synthesis was predominantly qualitative, with meta-analysis performed only when sufficient homogeneity was present among biomarker, population, and outcome definition.

4 RESULTS

The structured search in the pre-specified databases and registries was carried out with filters for free full text and a time frame limited to the last five years. During the consolidation stage of counts (identified records, duplicates removed, screening, and eligibility), the NCBI services used for automated and standardized counting were

unavailable, which prevented obtaining auditable global numbers for the PRISMA flowchart in this run.

Despite this operational limitation in counting, selection and clinical eligibility were completed normally, and 20 studies published within the last five years were included in the qualitative synthesis and fully composed Table 1, ordered from oldest to most recent, all focusing on biomarkers of endothelial injury/dysfunction and prognostic outcomes in sepsis/septic shock or equivalent contexts of infectious critical illness.

Table 1

Main included studies on endothelial injury biomarkers and prognosis in sepsis/septic Shock

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Piotti et al., 2021.	Adults with septic shock included in a multicenter study were evaluated for glycocalyx and endothelial junction biomarkers, with comparison between biomarker profiles and clinical outcomes.	Ninety-day mortality, organ failure, and need for renal replacement therapy were assessed.	Higher concentrations of syndecan-1 (Syndecan-1, SDC-1) and soluble VE-cadherin (Soluble VE-cadherin) were associated with greater severity and worse outcomes, suggesting that endothelial injury and barrier dysfunction contribute to poorer prognosis in septic shock.
Hatanaka et al., 2021.	Adults with sepsis in the intensive care unit had early SDC-1 measured and were compared according to development of persistent thrombocytopenia and clinical course.	Mortality and severity-related complications during intensive care unit stay were assessed.	Elevated SDC-1 levels were associated with endotheliopathy and worse course, supporting prognostic utility in sepsis during the early intensive care phase.
Yu et al., 2021.	Adults with sepsis and respiratory failure had endothelial biomarkers, including angiopoietin-2 (Angiopoietin-2, Ang-2), endocan (Endocan), soluble VE-cadherin, and SDC-1, evaluated and compared according to outcomes.	Severe acute kidney injury and adverse clinical outcomes, including mortality, were assessed.	Ang-2 showed the strongest independent association with acute kidney injury severity, while the biomarker panel as a whole indicated that endothelial dysfunction/injury is related to worse clinical evolution in sepsis.
Zhang et al., 2021.	Adults in intensive care with sepsis were compared with critically ill non-septic controls, with measurement of soluble thrombomodulin (Soluble Thrombomodulin, sTM) and an endothelial marker associated with fibrinolysis, with stratification by shock and coagulopathy.	Sixty-day mortality, occurrence of septic shock, and sepsis-associated coagulopathy were assessed.	Higher sTM levels were associated with worse prognosis and greater likelihood of septic shock and coagulopathy, supporting the prognostic role of early endothelial injury markers.
Zhou et al., 2022.	Adults in the intensive care unit with infection, sepsis, and septic shock were evaluated with serial measurement of SDC-1 and sTM and	Association with lactate, clinical severity, and adverse clinical outcomes was assessed.	SDC-1 and sTM increased with severity and correlated with markers of hypoperfusion and organ dysfunction, suggesting utility as endotheliopathy

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
	compared across severity groups.		markers in sepsis and septic shock.
Levy et al., 2022.	Adults with septic shock had endocan measured longitudinally, and biomarker trajectories were compared between survivors and non-survivors.	Mortality and association between temporal variation of endocan and outcomes were assessed.	Dynamic changes in endocan over the first week showed potential for risk discrimination, suggesting that serial measurements may add prognostic value in septic shock.
Tomášková et al., 2022.	Adults with septic shock had soluble endoglin (Soluble Endoglin, sEng) measured and were compared according to clinical outcomes.	Mortality and relationship with organ dysfunction and severity were assessed.	sEng was associated with worse prognosis, supporting its utility as a marker of endothelial activation/injury in septic shock.
Duyen et al., 2023.	Adults with sepsis in intensive care had angiopoietin-1 (Angiopoietin-1, Ang-1) and Ang-2 measured at different time points and were followed for clinical outcomes.	Progression to septic shock, association with Sequential Organ Failure Assessment (SOFA) and laboratory markers, and clinical outcomes were assessed.	Ang-2 increased with severity and correlated with SOFA and organ dysfunction markers, supporting pathophysiological relevance and potential prognostic value in sepsis.
Spoto et al., 2023.	Adults with sepsis or septic shock were evaluated with mid-regional proadrenomedullin (MR-proADM) and compared across severity strata and outcomes.	Twenty-eight-day mortality and association with clinical severity were assessed.	MR-proADM showed prognostic capacity for short-term mortality, suggesting clinical utility as a marker related to endothelial dysfunction and permeability.
Nguyen et al., 2023.	Adults with sepsis and septic shock according to contemporary criteria had sTM measured and were compared according to survival and severity.	Twenty-eight-day mortality and discriminative performance versus clinical scores were assessed.	Elevated sTM was observed in septic shock and in non-survivors, with prognostic performance comparable to clinical scores in discrimination analyses.
Aragão et al., 2024.	Critically ill adults with an infectious condition compatible with sepsis in intensive care had SDC-1 measured on admission and were compared according to vasopressor requirement and evolution.	Vasopressor requirement and hospital mortality were assessed.	Admission SDC-1 showed an independent association with vasopressor requirement and worse evolution, suggesting value as an early marker of endotheliopathy in infectious critical illness.
Hu et al., 2024.	Adults with sepsis in the intensive care unit had early SDC-1 measured and were compared according to 28-day survival, with adjustment for clinical and laboratory variables.	Twenty-eight-day mortality and performance in multivariable models were assessed.	SDC-1 was identified as a factor associated with 28-day mortality, and its incorporation into models with clinical severity and lactate added prognostic information.
Wejnaruemarn et al., 2024.	Adults with sepsis had endocan measured and were stratified according to organ dysfunction and clinical evolution during hospitalization.	Twenty-eight-day mortality and in-hospital mortality were assessed.	Elevated endocan was associated with greater organ dysfunction and higher mortality, supporting its role as a marker of severity and prognosis in sepsis.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Chen et al., 2024.	Adults with sepsis and cardiovascular involvement were randomized to pharmacologic modulation intervention and followed with serial measurements of heparanase (Heparanase, HPSE) and SDC-1, with comparison between groups.	Twenty-eight-day mortality, clinical severity, and serial endothelial markers were assessed.	The intervention was associated with reduction in HPSE and SDC-1 and with better clinical outcome, suggesting that reduction of glycocalyx injury may be related to better prognosis in septic subgroups.
Zhuo et al., 2024.	A systematic review and meta-analysis synthesized clinical studies in adults with sepsis that evaluated Ang-2 and mortality outcomes.	Mortality and overall predictive capacity of the biomarker were assessed.	Ang-2 showed consistent association with higher risk of death and moderate predictive performance, with heterogeneity attributed to timing of collection and clinical definitions.
Lipińska-Gediga et al., 2024.	Adults with septic shock had endocan measured serially and were compared according to hemodynamic parameters and clinical outcomes.	Mortality and association with organ dysfunction and need for hemodynamic support were assessed.	Serial endocan measurements showed association with severity and prognosis, suggesting utility for dynamic monitoring in septic shock.
Totoki et al., 2024.	Observational studies in adults with sepsis-associated disseminated intravascular coagulation compared combination therapy with antithrombin and soluble human thrombomodulin versus antithrombin alone or soluble human thrombomodulin alone.	Mortality and clinical outcomes related to recovery from disseminated intravascular coagulation were assessed, with quantitative synthesis when applicable.	Combination therapy was associated with improved outcomes in some studies, but evidence remained limited by heterogeneity and risk of bias, requiring cautious interpretation and prospective studies with standardized criteria.
Daniyarova et al., 2025.	A systematic review and meta-analysis evaluated glycocalyx and endothelial dysfunction markers in sepsis, with specific synthesis for mortality.	Mortality and consistency across studies for glycocalyx biomarkers were assessed.	SDC-1 and endocan showed association with mortality, with greater inter-study consistency for endocan, suggesting relatively better reproducibility among the evaluated markers.

5 RESULTS AND DISCUSSION

The study by Piotti et al. evaluated, in septic shock, a panel of biomarkers related to the endothelial glycocalyx and junction integrity, associating higher values with worse outcomes.[11] The internal consistency of the finding is supported by the multicenter design and the use of clinically relevant outcomes, such as mortality and organ failure.[11] In pathophysiological terms, the elevation of glycocalyx shedding markers suggests a phenotype of more pronounced permeability and microcirculatory dysfunction, which is consistent with worse prognosis in septic shock.[11] However, generalization depends on timing of collection and the degree of adjustment for severity, since early interventions may modify both inflammatory burden and biomarker levels.[12] In addition, immediate clinical applicability

is limited by the absence of standardized cutoff values and by analytical variability across laboratory platforms.[12]

In Hatanaka et al., early measurement of syndecan-1 in intensive care was associated with persistent thrombocytopenia and higher risk of death.[12] This finding is relevant because it links glycocalyx injury to a phenotype of endotheliopathy with hemostatic repercussions, frequently observed in more severe sepsis.[13] Still, because this is a setting in which multiple factors influence platelets and coagulation, interpretation requires caution regarding residual confounding.[13] From a clinical standpoint, the strength of this study lies in reinforcing that endothelial biomarkers may capture risk not fully explained by traditional parameters of systemic inflammation.[13] However, decision-making utility would depend on external validation and demonstration of prognostic increment over scores and lactate in pre-specified models.[14]

Yu et al. investigated endothelial biomarkers in sepsis with respiratory failure, showing a stronger association of angiopoietin-2 with acute kidney injury severity, in addition to relationships with clinical outcomes.[14] This result suggests that endothelial activation may function as a link between systemic inflammation, barrier dysfunction, and microvascular hypoperfusion culminating in renal dysfunction.[14] The main contribution of this work is to indicate that different biomarkers may behave differently according to target organ and predominant clinical phenotype.[15] However, heterogeneity in comorbidities, mechanical ventilation, and hemodynamic strategies may alter both endothelial biology and the probability of kidney injury, reducing direct comparability with other cohorts.[15] Furthermore, clinical translation requires clarity on the best time for collection and on whether serial measurements outperform a single baseline measurement in predictive capacity.[15]

In the study by Zhang et al., soluble thrombomodulin was higher in severe sepsis and was associated with mortality, septic shock, and coagulopathy, reinforcing that endothelial injury and hemostatic dysregulation occur together.[16] The strength of the work lies in integrating clinical outcomes with a marker plausibly linked to endothelial surface damage and loss of endogenous antithrombotic functions.[16] These findings are consistent with the contemporary understanding of immunothrombosis and endothelial dysfunction as key mechanisms of organ failure in sepsis.[16] Still, prognostic interpretation is sensitive to the definition of sepsis/septic shock, adjustment for severity, and concomitant anticoagulant management, which may influence both outcomes and markers.[17] In addition, reproducibility depends on comparable laboratory assays and validated cutoff values in external populations.[17]

Zhou et al. added evidence by evaluating serial measurements of syndecan-1 and soluble thrombomodulin, demonstrating increases proportional to severity and correlation with markers of hypoperfusion and organ dysfunction.[17] One valuable aspect is the serial approach, as it suggests that biomarker trajectory may reflect treatment response and the dynamics of endothelial injury.[18] At the same time, repeated measurements may capture fluctuations related to volume replacement, vasopressors, and ventilatory interventions, creating inevitable clinical heterogeneity.[18] The study reinforces that interpretation of endothelial biomarkers needs to consider timing, since a single measurement may have different meaning at admission versus after initial resuscitation.[18] Thus, prognostic utility may be greater when combined with clinical and laboratory variables rather than used as an isolated signal.[19]

Levy et al. evaluated endocan longitudinally in septic shock and observed that trajectories over the first week could discriminate risk.[19] This finding is conceptually important because it shifts the focus from a single baseline cutoff to dynamic patterns, potentially closer to the real course of critical illness.[19] Tomášková et al., in turn, reported an association of soluble endoglin with worse prognosis in septic shock, supporting that pathways of endothelial activation and vascular remodeling are also related to outcomes.[20] Together, these studies suggest that the endothelium is not a "single target," but rather a system with multiple biomolecular axes that may be activated at different intensities according to clinical phenotype.[20] However, the multiplicity of markers increases the risk of spurious results when multiple comparisons are performed without adequate adjustment, which must be weighed in critical appraisal.[20]

Duyen et al. explored angiopoietin-1 and angiopoietin-2 in sepsis in intensive care, showing that angiopoietin-2 tracked greater severity and correlated with SOFA.[21] This pattern is consistent with the biology of the Tie2 axis, in which angiopoietin-2 is associated with endothelial instability and increased permeability, favoring organ dysfunction.[21] The practical relevance of the study lies in suggesting that markers of endothelial activation may complement clinical scores by capturing processes that precede established organ failure.[21] However, clinical utility depends on demonstrating consistent incremental gain over SOFA and lactate in adjusted models and multicenter validations.[22] In addition, real-time use is hindered by test availability and laboratory turnaround time, especially in resource-limited settings.[22]

Spoto et al. evaluated MR-proADM in sepsis/septic shock and observed association with 28-day mortality, reinforcing the role of markers linked to permeability and vasoplegia as risk signals.[22] This result aligns with the concept that endothelial dysfunction and vascular

dysregulation may persist despite initial resuscitation, contributing to worse evolution.[23] Nguyen et al. analyzed soluble thrombomodulin in sepsis and septic shock, showing higher levels in non-survivors and prognostic performance comparable to clinical scores in discrimination analyses.[23] Together, these findings suggest that endothelial biomarkers may offer prognostic discrimination similar to scores, but with the potential advantage of reflecting specific mechanisms.[23] Even so, equivalence in performance does not guarantee clinical utility, since practical impact requires evidence that biomarker information changes management and improves outcomes.[24]

Aragão et al. demonstrated an association between admission syndecan-1 and vasopressor requirement, in addition to worse evolution, reinforcing utility as an early marker of endothelial instability in infectious critical illness.[24] The strength of this type of evidence lies in linking the biomarker to a highly clinical intermediate outcome representing hemodynamic severity and need for intensive support.[24] Hu et al. also found an association of syndecan-1 with 28-day mortality and suggested prognostic gain when incorporating it into models with severity and lactate.[25] These two studies together strengthen the hypothesis that glycocalyx markers may have incremental value, especially when used in an integrated rather than isolated way.[25] However, differences in population, timing of collection, and sepsis criteria may explain variations in effect magnitude across cohorts.[25]

Wejnaruemarn et al. evaluated endocan in sepsis and observed association with organ dysfunction and mortality, supporting the marker as an indicator of severity.[26] The clinical interest in endocan derives from its relationship with endothelial activation and inflammatory response, potentially reflecting risk of permeability and organ failure.[26] Still, like many endothelial biomarkers, endocan may rise in different critical conditions, which limits specificity when the goal is to differentiate infectious from non-infectious phenotypes.[26] From an implementation standpoint, utility would be greater if future studies explicitly compare endocan performance with SOFA and lactate in calibrated models with external validation.[27] In addition, assay standardization and definition of operational cutoff values are requirements for any consistent translational application.[27]

In the trial by Chen et al., an intervention with pharmacologic modulation was accompanied by reduction in heparanase and syndecan-1, with a signal of clinical improvement, suggesting that reducing glycocalyx injury may be related to better prognosis in subgroups.[27] The main value of this study is to offer a bridge between endothelial biomarkers and potential therapeutic targeting, going beyond observational prognostic association.[28] Zhuo et al. synthesized, in a systematic review and meta-analysis, the role of angiopoietin-2 in sepsis, reporting a consistent association with greater risk of death and

moderate predictive performance despite heterogeneity.[28] This synthesis strengthens the rationale for prioritizing angiopoietin-2 as a candidate in multimarker panels, especially when integrated with clinical variables.[28] However, heterogeneity in timing, analytical platform, and outcome definition may reduce the applicability of universal cutoff values.[29]

Lipińska-Gediga et al. emphasized the utility of serial endocan measurements in septic shock, suggesting that temporal dynamics may refine risk stratification.[29] Totoki et al., in a systematic review with meta-analysis on sepsis-associated disseminated intravascular coagulation, showed that therapeutic strategies related to endotheliopathy and hemostasis may influence outcomes, although limited by heterogeneity and risk of bias.[30] Daniyarova et al. synthesized evidence on glycocalyx and endothelial dysfunction markers, pointing to an association of syndecan-1 and endocan with mortality, with relatively better consistency for endocan in some scenarios.[30] Overall, certainty of evidence tends to vary from low to moderate, given the predominance of observational studies, inconsistency among methods, and imprecision in subgroups, reinforcing the need for prospective cohorts with standardized collection and pragmatic trials testing biomarker-guided strategies.[30]

6 CONCLUSION

The findings of this review indicate that markers of endothelial injury and dysfunction are consistently associated with severity and mortality in adults with sepsis and septic shock, especially when they reflect glycocalyx degradation and endothelial activation. Among the evaluated biomarkers, syndecan-1 and angiopoietin-2 were the most frequently linked to worse prognosis, whereas endocan, soluble thrombomodulin, and other markers showed variable utility according to population, timing of collection, and study design. Taken together, the evidence suggests that endothelial biology is a transversal component of the pathophysiology of infectious critical illness and may contribute to risk stratification beyond isolated clinical parameters. Even so, heterogeneity among studies limits direct comparisons and prevents the definition of universally applicable cutoff values. Thus, the synthesis points to a promising but still consolidating field for prognostic and translational application in intensive care.

From a clinical perspective, endothelial biomarkers may be useful as a complement to established scores and routine laboratory markers, particularly in scenarios in which the initial assessment underestimates the true risk or when prioritization of resources and intensified monitoring are required. Potential practical utility includes early identification of patients with greater likelihood of hemodynamic deterioration, progressive organ failure, and need for advanced support, in addition to supporting surveillance decisions and reassessment of

infectious source control. However, incorporation into routine practice should be cautious, since prognostic performance similar to that of clinical scores does not necessarily imply clinical benefit, and actual utility depends on how biomarker results alter management. In environments with limited access to specific tests and need for rapid responses, indices derived from routine tests may have operational advantage, although they also require external validation. Therefore, current clinical use is more appropriate as a stratification tool and support for clinical judgment rather than as an isolated determinant of intervention.

The main limitations of the literature include predominance of observational studies, risk of confounding by baseline severity and concomitant interventions, and relevant heterogeneity in clinical definitions, timing of collection, analytical platforms, and outcomes. Many studies used relatively small samples, with possible overestimation of effects and lower precision, in addition to multiple comparisons without uniform correction. The absence of standardization for laboratory assays and cutoff values hinders replication and comparability across centers, limiting immediate applicability. Moreover, most evidence does not answer whether integration of endothelial biomarkers into decision algorithms improves outcomes, leaving a gap between prognostic association and clinical impact. Thus, although biologically plausible and frequently associated with worse evolution, these markers have not yet reached sufficient methodological maturity for universal use.

Future research should prioritize prospective multicenter cohorts with standardized serial sampling, uniform definition of sepsis and septic shock, and clinically relevant outcomes, with pre-specified predictive models and external validation. Studies are also needed that systematically compare incremental performance over SOFA and lactate, including calibration, reclassification, and clinical utility, rather than discrimination alone. Pragmatic biomarker-guided trials with explicit management algorithms are essential to clarify whether interventions directed at endotheliopathy phenotypes alter outcomes and are cost-effective. Another priority is to develop multimarker panels and integrated strategies that capture different endothelial axes, evaluating which combinations generate greater robustness and applicability. Finally, efforts toward laboratory standardization and definition of operational cutoff values are essential for translation into practice.

In conclusion, endothelial injury represents a central pathophysiological axis in sepsis and septic shock, and its biomarkers emerge as promising tools for prognostic stratification in critically ill patients. Clinical adoption should be evidence-oriented, multidisciplinary, and individualized, recognizing current methodological limitations and avoiding decisions based on a single isolated marker. Consolidation of the field will depend on analytical standardization, external validation, and demonstration of incremental clinical benefit by

pragmatic studies, in addition to integration with clinical assessment and established protocols. By aligning biomarkers, clinical scores, and pathophysiological understanding, the path opens for more precise, risk-oriented, and potentially more efficient intensive care. This reinforces the importance of evidence-based strategies that connect biological mechanisms to clinical decisions, with a focus on improving outcomes in a population with high mortality and marked complexity.

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