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REVIEW

Biomarkers for the diagnosis and prognosis of sepsis according to its infectious source: a scoping review

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Abstract

Introduction: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. This study aimed to map and classify the biomarkers reported in the literature for the diagnosis and prognosis of sepsis, organizing them according to their frequency of occurrence in infections of the pulmonary, urinary, intra-abdominal, and skin and soft tissue origins.

Materials and methods: A scoping review was conducted following the PRISMA-ScR guidelines using the Population–Concept–Context (PCC) framework. Studies with systematic review designs, meta-analyses, and cohort studies published between January 2019 and June 2025 in English or Spanish were included. The search strategy was applied to PubMed, ScienceDirect, SciELO, and Google Scholar, using MeSH terms and keywords combined with Boolean operators (AND, OR).

Results: The most consistent biomarkers for pulmonary sepsis, including presepsin and sFLT-1, were used for diagnosis and endothelial dysfunction, whereas plasma gelsolin and transcriptomic profiles (OTOF, SIGLEC1, MS4A4A) provided prognostic value. For urinary sepsis, NLR, PLR, NGAL, and KIM-1 stand out for the detection of complications, such as AKI, while presepsin and lactate were confirmed as robust prognostic markers. In abdominal sepsis, IL-18 and PSP emerge as complementary markers for differentiating foci and predicting complications, and CRP and PCT are useful in combination. For skin and soft tissue infections, YKL-40 and the lactate/albumin ratio show potential, although validation is lacking.

Discussion: The transition from classical biomarkers to emerging tools with potential in precision medicine has been confirmed, such as transcriptomic profiles and molecular technologies, which are particularly useful in the pulmonary and abdominal settings.

Keywords: Sepsis; biomarkers; infectious focus; scoping review; diagnosis; prognosis

Biomarcadores para diagnóstico y pronóstico de sepsis según su foco infeccioso: una revisión de alcance

Resumen

Introducir: La sepsis se define como una disfunción orgánica potencialmente mortal causada por una respuesta desregulada del huésped a la infección. Este estudio tuvo como objetivo mapear y clasificar los biomarcadores reportados en la literatura para diagnóstico y pronóstico de la sepsis, organizándolos según su frecuencia de aparición en infecciones de origen pulmonar, urinario, intraabdominal y de piel y tejidos blandos.

Materiales y métodos: Se realizó una revisión de alcance siguiendo la guía PRISMA-ScR, utilizando el marco PCC (Population–Concept–Context). Se incluyeron estudios con diseño de revisión sistemática, metaanálisis y estudios de cohorte publicados entre enero de 2019 y junio de 2025, en inglés o español. La estrategia de búsqueda se aplicó en PubMed, ScienceDirect, SciELO y Google Scholar, empleando términos MeSH y palabras clave combinadas con operadores booleanos (AND, OR).

Resultados: Los biomarcadores más consistentes para sepsis pulmonar incluyen presepsina y sFLT-1 para diagnóstico y disfunción endotelial, mientras que la gelsolina plasmática y perfiles transcriptómicos (OTOF, SIGLEC1, MS4A4A) aportan valor pronóstico. Para sepsis urinaria, NLR, PLR, NGAL y KIM-1 se destacan para detección de complicaciones como AKI; presepsina y lactato se confirman como marcadores pronósticos sólidos. En sepsis abdominal, IL-18 y PSP surgen como complementos para diferenciar focos y predecir complicaciones; PCR y PCT son útiles combinados. Para infecciones de piel y tejidos blandos, YKL-40 y la relación lactato/albúmina muestran potencial, aunque falta validación.

Discusión: Se confirma la transición desde biomarcadores clásicos hacia herramientas emergentes con potencial en medicina de precisión, como perfiles transcriptómicos y tecnologías moleculares, especialmente útiles en contextos pulmonares y abdominales. Conclusión: Ningún biomarcador debe interpretarse de forma aislada; se requiere más investigación multicéntrica para validar paneles combinados y enfoques ómicos, fortaleciendo la precisión diagnóstica y pronóstica en la atención integral de la sepsis.

Palabras clave: Sepsis; biomarcadores; foco infeccioso; revisión de alcance; diagnóstico; pronóstico

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Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. This systemic inflammatory response is heterogeneous and multifactorial, combining processes such as hyperinflammation, endothelial damage, coagulopathy, and phases of immunosuppression, which together influence the patient's clinical course and prognosis[2]. Despite therapeutic advances, sepsis continues to have a high mortality rate, particularly when it is associated with septic shock. According to recent estimates from the Global Burden of Disease, supported by the World Health Organization, sepsis affects approximately 49 million people annually and is associated with more than 11 million deaths each year worldwide, accounting for nearly 20% of all global deaths[3]. In this context, biomarkers have become essential complementary tools for improving diagnostic accuracy and risk stratification in patients with suspected sepsis. Traditional markers, such as C-reactive protein (CRP), procalcitonin (PCT), and lactate, are widely used to support the identification of bacterial infections, assess the responses to antibiotic therapy, and guide resuscitation strategies[4]. However, their performance in isolation has limitations related to specificity, sensitivity, and the ability to distinguish between bacterial infections and non-infectious inflammatory processes. Moreover, their usefulness may vary depending on the primary infectious focus and magnitude of local and systemic inflammatory responses.

In recent years, research on emerging biomarkers has led to the identification of promising molecules that reflect different aspects of sepsis pathophysiology[5]. These include soluble fragments, such as presepsin, peptides associated with endothelial dysfunction, and novel approaches based on transcriptomic signatures and omics profiles, such as the sepsis response signature 1 (SRS1) and sepsis response signature (SRS2) endotypes[6], which aim to capture immunological heterogeneity of the host response. The integration of these biomarkers with clinical parameters, severity scores, and microbiological findings offers a pathway toward precision medicine by enabling more personalized risk stratification and dynamic monitoring of patients with sepsis.

Given that inflammatory profiles and biomarker kinetics can vary depending on whether the infection originates from the lungs, urinary tract, abdomen, or skin and soft tissues[7], it is pertinent to conduct a structured synthesis of the available evidence to identify the most frequently reported and studied biomarkers for each specific focus. This approach could help clinicians select the most appropriate biomarkers based on the clinical context, optimize decision-making algorithms, and strengthen the design of individualized therapeutic strategies.

In light of this need, the present scoping review aimed to map and classify the biomarkers described in the scientific literature for the diagnosis and prognosis of sepsis, organizing them according to their frequency of occurrence in pulmonary, urinary, intra-abdominal, skin, and soft tissue infections.

Materials and methods

This review was conducted following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines[8]. A scoping review design was considered appropriate because of the heterogeneity of existing biomarkers and the need to map knowledge areas, identify gaps, and describe the distribution of the available evidence. The protocol and registration according to PRISMA-ScR can be found in Supplementary Material 1.

The research question was structured using the PCC framework: P (Population): Patients with sepsis, C (Concept): Biomarkers used for diagnosis and prognosis, and C (Context): Classified according to their frequency of reporting in different infectious sources—pulmonary, urinary, intra-abdominal, and skin and soft tissue infections. Based on these elements, the research question of this review was: "What biomarkers have been reported in the literature for the diagnosis and prognosis of sepsis, and how are they distributed according to their frequency of appearance across different infectious sources?"

A systematic and reproducible search strategy was designed to identify relevant studies on biomarkers used for the diagnosis and prognosis of sepsis, organized by the site of infection. The search was conducted in the PubMed, ScienceDirect, SciELO, and Google Scholar databases, covering the period from January 2019 to June 2025, to include recent and high-quality evidence.

MeSH terms and keywords were combined using the Boolean operators AND and OR, and the syntax was adapted for each of the databases. Specific filters were also applied to limit the search to systematic reviews, meta-analyses, and cohort studies, as these designs offer a higher level of evidence for mapping biomarkers.

The main search terms included: ("sepsis") AND ("gene expression profile"), ("Preoperative inflammatory biomarkers" OR "biomarkers") AND ("systemic inflammatory response syndrome" OR "SIRS") AND ("systematic review" OR "meta-analysis" OR "cohort study"), ("Biomarkers" OR "biomarker") AND ("sepsis") AND ("urinary") AND ("systematic review" OR "meta-analysis" OR "cohort study"), ("Biomarkers" OR "biomarker") AND ("sepsis") AND ("systematic review" OR "meta-analysis" OR "cohort study").

These strategies were adapted to each database according to its specific syntax and filter. An additional search was performed on Google Scholar to identify gray literature and studies that were potentially not indexed in the main databases. The search was limited to publications in English and Spanish languages.

The inclusion criteria for this scoping review were studies with rigorous methodological designs, such as systematic reviews, meta-analyses, and cohort studies, given their potential to provide robust evidence on biomarkers in sepsis. The included studies evaluated patients diagnosed with sepsis of any infectious origin, including pulmonary, urinary, intra-abdominal, and skin and soft tissue infections, with no restrictions on age or sex. The selected studies reported biomarkers used for diagnostic and/or prognostic purposes in the context of sepsis, indicating, when possible, their association with the specific site of infection. The timeframe for the search spanned January 2019 to June 2025, and only articles published in English or Spanish with full-text availability were accepted. The excluded studies included duplicates, letters to the editor, commentaries, editorials, protocols without results, studies based exclusively on animal models or in vitro research, publications without access to the full text, and those that did not provide specific information about biomarkers used for the diagnosis or prognosis of sepsis.

The study selection for this scoping review was conducted in two successive phases. In the first phase, two independent reviewers screened the titles and abstracts of all retrieved records to assess eligibility based on predefined criteria. In the second phase, potentially relevant studies were evaluated in full text to confirm their final inclusion criteria. Any discrepancies between the reviewers were resolved by consensus, and when necessary, a third reviewer was consulted to resolve disagreements.

The studies were selected independently by two reviewers (VL and RA). In the first phase, both reviewers screened the titles and abstracts of records identified in PubMed, ScienceDirect, SciELO, and Google Scholar, applying predefined inclusion and exclusion criteria. Any discrepancies were resolved through consensus. In cases where agreement could not be reached, a third reviewer (LT) was consulted for the final decision.

For data extraction, a structured table was developed to systematize the information obtained from each study. The following data were systematically extracted: study title, author(s), year of publication, country where the research was conducted, methodological design (systematic review, meta-analysis, or cohort study), type of biomarker reported (classified as classical or omics-based), associated infectious source (pulmonary, urinary, intra-abdominal, skin, or soft tissue), relevant findings related to its diagnostic and/or prognostic utility in sepsis, and the reported source of funding. Funding information was categorized as follows: (1) industry, (2) government, (3) academic or university-based, (4) nonprofit organization or foundation, (5) mixed funding (a combination of the previous categories), (6) not reported, or (7) explicit statement of no funding received.

Results

In total, 16 studies were included and distributed across different infectious sources of sepsis. Table 1 summarizes the main characteristics of these studies, including the study design, reported biomarkers, and relevant findings for diagnosis and prognosis.

Of these, three studies (18.7%) explicitly declared that they had received no funding, while two studies (12.5%) did not provide any information regarding financial support. Of the 11 studies (68.7%) that reported funding sources, government support was the most frequently identified (n = 7, 43.7%), followed by academic funding (n = 2, 12.5%) and industry participation (n = 2, 12.5%). Additionally, one study (6.2%) reported mixed funding from government and foundation sources. These results suggest that most research on sepsis biomarkers categorized by infectious source is predominantly sustained by public funding, with a comparatively limited contribution from the private industry. Further details of the funding classification for each included study are available in Supplementary Material 2.

This table summarizes the infectious focus addressed, study title, author, year of publication, country, study design, type of biomarker (classical or emerging), sample collection site, and relevant findings regarding its diagnostic and/or prognostic utility.

The study selection process was conducted in accordance with the PRISMA-ScR guidelines and is summarized in Figure 1. A total of 200 records were initially identified through database searches, with no additional records obtained from other sources. After the removal of 30 duplicate records, 170 studies remained for title and abstract screening, of which 110 were excluded based on the predefined criteria.

Subsequently, 60 full-text articles were retrieved, and 55 were successfully assessed for eligibility after excluding five reports that could not be retrieved. Of these, 39 studies were excluded for specific reasons: lack of differentiation between infectious sources (n = 24), lack of reporting of diagnostic or prognostic biomarkers (n = 10), and absence of prognostic biomarkers (n = 5).

Ultimately, 16 studies met the inclusion criteria and were included in the final analysis. This stepwise selection process ensured systematic, transparent, and reproducible identification of relevant studies.

Biomarkers reported for the diagnosis and prognosis of sepsis were mapped and classified according to the infectious focus, with the aim of identifying differential patterns in their expression and clinical utility based on the origin of infection. In Figure 2, the main biomarkers of sepsis are illustrated according to their infectious sources. This classification allows for a more precise analysis of the most relevant biomarkers in specific clinical contexts[9].

First, in the case of pulmonary infections, among the reviewed biomarkers, presepsin (sCD14-ST)[10] stands out as one of the most promising markers for early sepsis diagnosis, particularly for differentiating between septic and non-septic inflammatory conditions. Assal et al. demonstrated that a baseline level above 775 pg/mL is associated with high discri-

Table 1. Characteristics of the studies included in the scoping review

Infectious focus	Title	Author	Year	Country	Study design	Classic Biomarker	Emerging Biomarker	Biomarker sampling site	Findings
Pulmonary	A Systematic Review of Gene Expression Studies in Critically Ill Patients with Sepsis and Community-Acquired Pneumonia[6]	Viasus D, Nonell L, et al.	2023	Spain	Systematic Review	X	SRS1 y SRS2, FAIM3:PLAC8, miARN	SRS1/SRS2 y FAIM3:PLAC8 (Blood), miARN (Plasma)	Transcriptomic analysis in sepsis due to community-acquired pneumonia (CAP) identified two immune signatures (SRS1 and SRS2) with different mortality rates (22% vs. 10%). Additionally, elevated levels of miR-1246 were associated with greater severity, while miR-193a-5p and miR-542-3p distinguished between infection and healthy subjects, demonstrating diagnostic utility.
	Low Admission Plasma Gelsolin Concentrations Identify Communityacquired Pneumonia Patients at High Risk for Severe Outcomes[15]	Self WH, Wunderink RG, Fakhran S, Cao B, Balk R, Sethi S, et al.	2019	United States	Nested prospective observational cohort study	X	pGSN	Plasma	Plasma gelsolin (pGSN) functions as a "scavenger" protein for extracellular actin released during cellular injury, modulating systemic inflammation and supporting pulmonary immune defense. Low pGSN concentrations (≤32.1 µg/mL) at admission were associated with a higher risk of requiring vasopressor or ventilatory support (24.8%) and increased mortality (8.8%) in patients with community-acquired pneumonia (CAP). pGSN demonstrated prognostic utility in identifying severe cases and candidates for immunomodulatory therapies.
	Valor del biomarcador tirosina quinasa 1 soluble tipo fms (sFLT-1) en el diagnóstico y pronóstico de la sepsis: una revisión sistemática[13]	Ugaldea MJ, Caballero A, Fernández M, López D, Pérez J, et al.	2024	Spain	Systematic Review	X	sFLT-1	Blood	sFLT-1 was significantly elevated in sepsis and septic shock, correlating with organ dysfunction, clinical severity (SOFA, APACHE II), and mortality (AUC up to 0.87). It demonstrated differential diagnostic utility compared to other causes of shock and showed consistent prognostic value across various populations, including diabetic, immunosuppressed, and COVID-19 patients.
	Presepsin as a Novel Biomarker in predicting Inhospital Mortality in Patients With COVID-19 Pneumonia[11]	Assal HH, Abdelrahman SM, Abdallah MA, Ahmed M, Ibrahim I, et al.	2022	Saudi Arabia and Egypt	Original multicenter retrospective cohort study	X	Presepsin	Blood (Serum)	Presepsin levels >775 pg/mL were associated with higher in-hospital mortality in patients with COVID-19 pneumonia (sensitivity 73%, specificity 80%) and the need for ICU admission. It outperformed other inflammatory markers (CRP, ferritin, NLR) as a prognostic predictor in pulmonary sepsis.
	Prospective multicenter study identifying prognostic biomarkers and microbial profiles in severe CAP using BALF, blood mNGS, and PBMC transcriptomics[17]	Song W, Yang Q, Lv H, Lv Y, Jiang Y, Qu J, et al.	2025	China	Prospective multicenter observationa l study	X	BALF mNGS vs sangre mNGS vs CMT	Bronchoalveol ar Lavage Fluid, Blood	In patients with severe communityacquired pneumonia (SCAP), elevated expression of the genes OTOF, SIGLEC1, MS4A4A, and CXCL10— identified through bulk RNA sequencing of PBMCs—was associated with poor prognosis and higher mortality. These transcriptomic biomarkers, detected as part of an integrated mNGS approach, reflect immune dysfunction and excessive inflammatory activation, and may serve as prognostic indicators in pulmonary sepsis.

Urinary	Preoperative inflammatory biomarkers analysis in prognosis of systemic inflammatory response syndrome following percutaneous nephrolithotom y: A systematic review and meta-analysis[21]	Noviardi, D.E.P.P.et al.	2022	Indonesi a	Systematic Review and MetaAnalysis	PCR	X	Blood (Serum)	In patients undergoing percutaneous nephrolithotomy (PCNL), elevated preoperative levels of CRP, NLR, and PLR were significantly associated with a higher risk of developing postoperative sepsis. A PLR >120.5 showed 81% sensitivity and 80.1% specificity. These inflammatory biomarkers help predict septic complications in urinary sepsis.
	Biomarkers for the diagnosis of sepsis-associated acute kidney injury: systematic review and meta-analysis[26]	Xie Y, Huang P, Zhang J, et al.	2021	China	Systematic Review and MetaAnalysis	KIM-1,NGAL, IL-18	X	NGAL Urine and Blood (Serum), KIM-1 and IL18 in Urine	In this systematic review and meta-analysis, biomarkers used to diagnose sepsis-associated acute kidney injury (AKI) were evaluated. Urinary KIM-1 demonstrated the highest diagnostic accuracy (AUC 0.931; sensitivity ≈ 86%, specificity ≈ 84%), followed by urinary NGAL (AUC 0.907). These biomarkers outperformed blood NGAL and urinary IL-18, supporting their role as useful diagnostic indicators in sepsis-associated renal injury.
	Presepsin as a predictor of septic shock and mortality in patients with urinary tract infection according to the Sepsis-3 definitions[27]	Yang GB, Lee KR, Hong DY, Park SO, Kim JW, Kim SY, et al.	2024	South Korea	Prospective observationa l cohort	PCT, CRP, lactato, WBC	Presepsin	Blood	In patients with urinary tract infections, elevated presepsin levels at admission were independently associated with an increased risk of septic shock (AUC 0.739, cutoff 447 pg/mL) and 30-day hospital mortality (AUC 0.744, cutoff 709 pg/mL), according to Sepsis-3 criteria. Its performance surpassed that of PCT and CRP.
	Related factors of bloodstream infections associated with urinary tract infections and pathogenetic characteristics analysis[22]	Shao Y, Jia W, Li G.	2024	China	Retrospectiv e observational study	Neutrophils, NLR, Lactate, CRP, total proteins and albumin.	X	Blood	In patients with urinary sepsis, the biomarkers NLR, lactate, and neutrophil percentage (N%) demonstrated high diagnostic utility for predicting septic shock (AUC: 0.775, 0.772, and 0.773, respectively). Predictive value improved when these markers were combined. NLR and lactate were independent predictors of progression to severe sepsis.
	Comparing the Prognostic Value of Lactate to the Neutrophil-to-Lymphocyte Ratio Among Sepsis Patients: A Prospective Cohort Study[29]	Bou Chebl R, Haidar S, Kattouf N, Assaf M, Alwan JS, Khamis MM, et al.	2025	Lebanon	Prospective observational cohort	Lactate, NLR	X	Blood	In this prospective cohort of 874 patients with sepsis or septic shock, serum lactate was significantly associated with in-hospital mortality (OR=1.188; p<0.0001), whereas the neutrophil-tolymphocyte ratio (NLR) showed no association (OR=1.003; p=0.544). Lactate outperformed NLR in subgroups such as urinary sepsis, patients under 65 years of age, and those with albumin levels <30 g/L.
Skin and Soft Tissues	Associations between 40 markers disease severity death patients necrotizing soft-tissue infection[39] YKLand of and in with	Hedetoft M, Hansen MB, Madsen MB, Johansen JS, Hyldegaard O.	2021	Denmar k	Prospective observational cohort	X	YKL-40	Blood (Serum)	In patients with necrotizing soft tissue infection, plasma YKL-40 was associated with greater clinical severity, the need for renal replacement therapy, and an increased risk of 30-day mortality. However, after adjusting for SAPS II, YKL-40 was not an independent predictor of death, although it may have value as an early marker of severity.

	Utility of the Lactate/ Albumin Ratio as a Predictor for Mortality in Necrotizing Fasciitis Patients[40]	Lau KK, Hsiao CT, Fann WC, Chang CP	2021	Taiwan	Observational retrospective cohort	Lactato y Albúmina (L/A ratio)	X	Blood	In patients with necrotizing fasciitis, the lactate/albumin (L/A) ratio predicted inhospital mortality more accurately than lactate alone (AUROC 0.76 vs. 0.71). This prognostic value remained significant even in patients with normal lactate levels. An L/A ratio ≥1.61 was significantly associated with higher mortality, regardless of other clinical variables.
Intra-abdominal	Evaluación de la proteína C reactiva, la procalcitonina y el índice PCR/PCT como indicadores de mortalidad en sepsis abdominal[36]	Godínez-Vidal A, Alcántara Gordillo R, et al.	2020	Mexico	Retrospective, observational, correlational, analytical, cross-sectional study	PCR Y PCT	X	Blood (Serum)	In patients with abdominal sepsis, CRP levels were significantly higher in nonsurvivors (328 vs. 170 mg/L; p=0.001), while PCT showed no significant differences (17.6 vs. 10.5 ng/mL; p=0.460). The CRP/ PCT index was markedly higher in non-survivors (7534 vs. 538; p=0.001), standing out as a better predictor of mortality.
	Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin for post-operative sepsis/ infection in liver transplantation[37]	Jerome E, et al.	2022	United Kingdom	Systematic Review and MetaAnalysis	PCT	X	Blood (Serum)	In patients undergoing liver transplantation, procalcitonin (PCT) demonstrated a sensitivity of 70% and a specificity of 78% for diagnosing postoperative sepsis, with an AUC of 0.871. Its performance was better in adults, effectively distinguishing between bacterial infection and acute rejection. It outperformed CRP and WCC in this context.
	The Role of the Pancreatic Stone Protein in Predicting Intra-Abdominal Infection- Related Complications: A Prospective Observational Single-Center Cohort Study[34]	Michailides C, Lagadinou M, Paraskevas T, Papantoniou K, Kavvousanos M, Vasileiou A, et al.	2023	Greece	Prospective observational cohort	X	PSP	Blood (Serum)	In patients with intra-abdominal infections, pancreatic stone protein (PSP) was an independent predictor of sepsis (adjusted OR 7.88; p=0.028), readmission (AUC 0.899), and treatment escalation (AUC 0.862). It outperformed CRP, ferritin, and fibrinogen in these outcomes, demonstrating high sensitivity and prognostic value within the first 24 hours.
	Diagnostic Utility of IL18 Plasma Levels in Distinguishing Abdominal from NonAbdominal Sepsis[32]	Herminghaus A, Totskyi M, Vollmer C, Dimski T, Brandenburger T, Kuebart A, et al.	2025	Germany	Prospective–retrospective cohort	PCR, PCT	IL-18	Blood	In patients with sepsis, plasma IL-18 levels were significantly higher in non-abdominal sepsis, demonstrating diagnostic utility in differentiating the site of infection (AUC 0.68; cutoff <1892 pg/mL, sensitivity 82.6%). IL-18 correlated with disease severity (SOFA), mortality, and other biomarkers (IL-6, IL10, MCP-1).

minative power for in-hospital mortality (AUC 0.84), with a sensitivity of 73% and specificity of 80%, and correlates with clinical scales such as the Pneumonia Severity Index (PSI) and Neutrophil-Lymphocyte Ratio (NLR)[11].

Similarly, soluble fms-like tyrosine kinase-1 (sFLT-1)[12] is emerging as a key biomarker of endothelial dysfunction, with differential diagnostic utility for distinguishing sepsis from other shock syndromes. Ugalde et al. reported persistently elevated sFLT- 1 levels to be associated with increased severity, multiorgan dysfunction, and mortality prediction (AUC up to 0.87)[13].

In contrast, plasma gelsolin (pGSN)[14] has demonstrated robust prognostic value for adverse outcomes in community-acquired pneumonia (CAP). Self et al. found that low plasma concentrations at admission (≤32.1 µg/mL) were associated with a ninefold increased risk of death, greater need for respiratory and vasopressor support, and longer hospital stay[15]. Moreover, in the transcriptomic domain, genes and molecular signatures with potential prognostic value in severe community-acquired pneumonia (CAP) have been identified[16]. Song et al. highlighted OTOF, SIGLEC1, and MS4A4A as gene markers associated with mortality, while FOLR3 and ITGA7 were consistently linked to pneumonia severity.

These profiles, along with the identification of poor-prognosis pathogens (Pneumocystis jirovecii, Human Cytomegalovirus (HCMV), and Corynebacterium striatum), support the integration of transcriptomics and metagenomics as complementary tools for risk stratification[17]. Additionally, the use of next-generation metagenomic sequencing (mNGS) in Bronchoalveolar lavage fluid (BALF)[18] samples enabled more accurate detection of bacteria (such as Acinetobacter baumannii and Klebsiella pneumoniae), fungi (Candida spp. and Pneumocystis jirovecii), and viruses (HCMV, Epstein-Barr Virus (EBV), Torque teno virus (TTV)), improving etiological characterization compared to conventional methods. This microbiological information, when integrated with plasma and transcriptomic biomarkers, enhances both the diagnostic and prognostic capabilities of sepsis of pulmonary origin[17].

Second, in the urinary context, hematologic indices such as the neutrophil-to-lymphocyte ratio (NLR)[19] and platelet-to-lymphocyte ratio (PLR)[20] have shown high predictive value for postoperative urinary sepsis, particularly in patients undergoing percutaneous nephrolithotomy. Noviardi et al. found that leukocyte count (MD 0.69), NLR (MD 0.59), and PLR (MD 23.4) were significantly correlated with the risk of SIRS and urosepsis following surgery, with statistically significant differences (p < 0.00001) (21). Furthermore, in cases of urosepsis progressing to shock, Shao et al. reported that NLR and neutrophil percentage (N%) are useful parameters for severity stratification. NLR showed an AUC of 0.775 (95% CI: 0.686–0.863), and N% had an AUC of 0.773 (95% CI: 0.684–0.863) for distinguishing patients with urinary septic shock[22].

In line with the above, regarding urinary sepsis[23] complicated by acute kidney injury (SA-AKI), Xie et al. demonstrated that urinary neutrophil gelatinase-associated lipocalin (NGAL) and urinary kidney injury molecule-1 (KIM-1)[24] provide the highest diagnostic value. Urinary KIM-1 had a summary receiver operating characteristic (SROC) (25) of 0.931 with 86% sensitivity and 84% specificity, whereas urinary NGAL showed an SROC of 0.907. These values surpassed those of serum NGAL (SROC 0.857) and urinary IL-18 (SROC 0.861)[26].

It is worth noting that presepsin (sCD14-ST) is emerging as one of the most promising plasma biomarkers for urosepsis. In a prospective study, Yang et al. found that presepsin was an independent predictor of septic shock (OR 1.002; 95% CI: 1.001– 1.002; p < 0.001) and 30-day in-hospital mortality (HR 1.0005; 95% CI: 1.0001–1.001; p = 0.03) in patients with urinary tract infections, with an AUC of 0.739 for septic shock and 0.744 for mortality[27]. Similarly, Bou Chebl et al. compared serum lactate levels[28] and NLR for predicting mortality in patients with sepsis, including subgroups with urinary infections. Lactate level was independently associated with in-hospital mortality (OR 1.188; 95% CI: 1.086–1.299; p < 0.0001), whereas NLR showed no significant association (OR 1.003; p = 0.544). Moreover, lactate demonstrated a higher AUC (0.70) than NLR (0.55) in patients with urinary-source sepsis, indicating it as a more robust prognostic biomarker[29]. Shao et al. evaluated the utility of combined biomarkers (N%, NLR, lactate, PT, and albumin). The combination showed better performance in detecting urinary septic shock than individual biomarkers, with an AUC of 0.863, sensitivity of 80.8%, and specificity of 83.1%[22].

Regarding sepsis of abdominal origin, the reviewed studies described various biomarkers evaluated as tools for diagnosis, identification of the infectious source, and prognosis in patients with intra-abdominal infection[30]. Herminghaus et al. explored the usefulness of IL-18, along with other mediators such as IL-6, MCP-1, and IL-10, to differentiate patients with abdominal sepsis from those with sepsis of other origins. The authors reported that plasma IL-18[31] levels were significantly lower in abdominal sepsis compared to non-abdominal sources and that, although the discriminative capacity of IL-18 was moderate (AUC approximately 0.68), it could serve as a complementary marker in source differentiation when combined with other inflammatory biomarkers[32]. This finding supports the hypothesis that the inflammatory response and cytokine kinetics may vary depending on the infection site[33], highlighting the importance of contextualizing the interpretation of these markers.

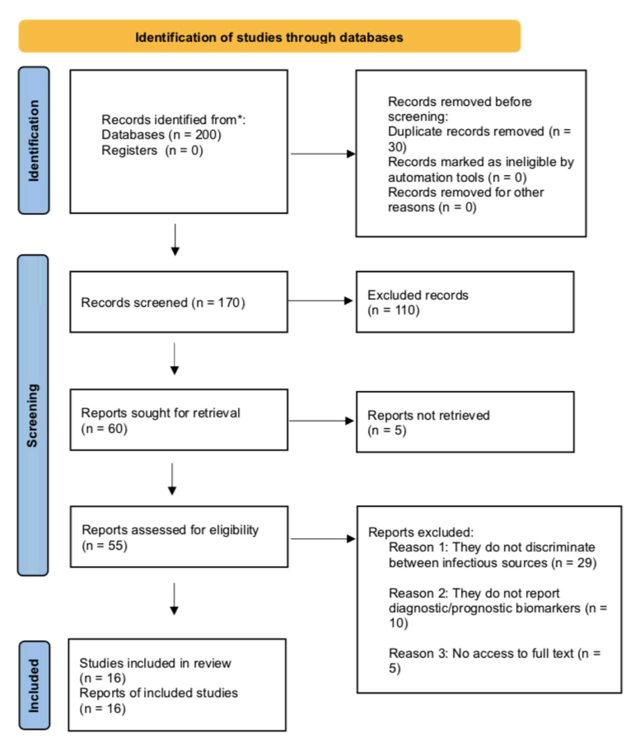

Figure 1. The study selection process was conducted in accordance with the PRISMA-ScR guidelines.

In contrast, Michailides et al. evaluated Pancreatic Stone Protein (PSP) as an emerging biomarker in a prospective cohort of patients with intra-abdominal infections. PSP levels were measured at admission and demonstrated robust predictive value for infection-related complications, including the development of sepsis, need for escalation of antibiotic therapy, prolonged hospital stay, and likelihood of readmission. PSP outperformed other parameters, such as C-reactive protein (CRP), ferritin, and fibrinogen, in terms of discriminative capacity, with area under the curve (AUC) values ranging from approximately 0.86 to 0.90 for certain outcomes. These results suggest that PSP could be incorporated as part of a biomarker panel to improve early risk stratification in intra-abdominal infections, although the authors acknowledge that multicenter studies are needed to validate the standardized cut-off values[34].

Regarding more established biomarkers, Godínez-Vidal et al. conducted a retrospective study in surgical patients with secondary peritonitis and sepsis, analyzing the utility of CRP, procalcitonin (PCT), and the combined CRP/PCT index as mortality predictors. The results showed that elevated CRP levels

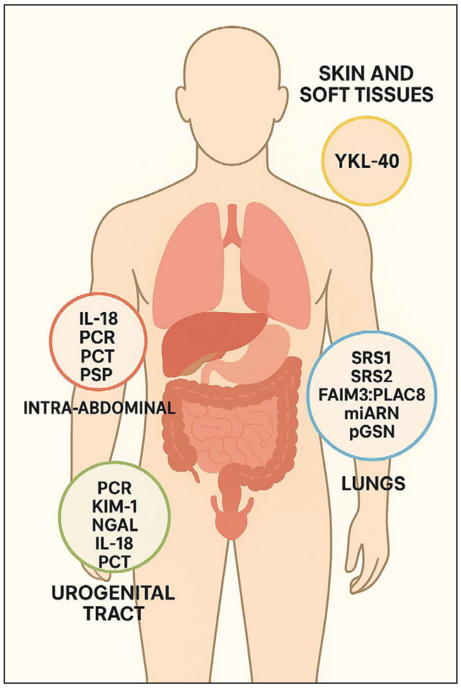

Figure 2. Biomarkers in sepsis according to its infectious focus. Image of own authorship.

were significantly associated with an increased risk of death, whereas PCT[35] alone did not consistently demonstrate a strong association at all measurement points. However, the combination of both markers in the form of a CRP/PCT index improved the discriminatory ability to predict in-hospital mortality, suggesting that the integrated interpretation of classical biomarkers can enhance outcome prediction in abdominal sepsis[36].

Similarly, a meta-analysis by Jerome et al. assessed the accuracy of PCT as a biomarker in patients undergoing liver transplantation, a clinical setting considered a model for postoperative intra-abdominal infections. The review pooled data on sensitivity and specificity, finding that PCT achieved approximately 70% sensitivity and approximately 78% specificity for detecting postoperative sepsis. Although PCT showed moderate utility as a diagnostic aid, the authors emphasized that its performance depends on the timing of measurement and the cut-off value used; therefore, it is recommended to use it in combination with clinical variables and other laboratory parameters[37].

Regarding skin and soft tissue infections, Hedetoft et al. investigated the utility of YKL-40 (chitinase-3-like protein 1, CHI3L1)[38], a protein secreted by activated immune cells, as a prognostic biomarker in patients with necrotizing soft tissue infections (NSTIs) who developed severe sepsis. The results showed that plasma YKL-40 levels were significantly higher in patients with NSTIs who developed septic shock (median: 1942 ng/mL) than in those without shock (720 ng/mL; $p < 0.001$). Elevated levels are also associated with an increased need for renal replacement therapy, a common complication of severe sepsis[39].

A YKL-40 level above 1840 ng/mL was linked to a higher 30-day mortality risk (OR 3.77; 95% CI: 1.59–9.24; $p = 0.003$) in models adjusted for age, sex, and comorbidities, although this association lost statistical significance after adjusting for severity scores, such as the simplified Acute Physiology Score II (SAPS II). The AUC of YKL-40 (0.64) was lower than that of SAPS II (0.86) and lactate (0.80), suggesting that its greatest utility lies in complementing the monitoring of sepsis severity associated with NSTI rather than serving as an independent predictor of mortality[39].

In necrotizing fasciitis, Lau et al. evaluated the lactate-to-albumin (L/A) ratio as a predictor of mortality in patients with sepsis associated with NF. In a retrospective analysis of 262 patients, the L/A ratio demonstrated a better ability to predict in-hospital mortality (AUROC 0.76) than lactate alone (AUROC 0.71). The optimal cutoff point was 1.61, with a sensitivity of 75% and a specificity of 81% for mortality prediction[40].

Importantly, the prognostic value of the L/A ratio remained significant even in patients with normal lactate levels, positioning it as a sensitive indicator for identifying severe sepsis cases that might otherwise go unrecognized. The presence of hypoalbuminemia further enhances the discriminative power of this ratio as a composite biomarker for risk stratification in sepsis secondary to skin and soft tissue infections[40].

Despite these findings, data on specific biomarkers for the diagnosis and prognosis of sepsis originating from skin and soft-tissue infections remain scarce. The available studies have limited sample sizes, lack multicenter validation, and show poor standardization of clinically applicable cutoff values. This gap highlights the need for larger studies to confirm the utility of these markers and their integration into the sepsis management algorithms.

Discussion

The biomarkers with the greatest diagnostic predictive power in pulmonary-origin sepsis were presepsin and sFLT-1, highlighting their usefulness in distinguishing septic states and stratifying the risk of early mortality. As prognostic predictors, plasma gelsolin, transcriptomic profiles (OTOF, SIGLEC1, MS4A4A), and microbial characterization through mNGS have emerged as key tools for identifying patients at a higher risk of adverse outcomes, complementing clinical assessment and supporting precision medicine approaches.

The findings indicate that for diagnostic purposes, NLR, PLR, leukocyte count, and urinary biomarkers such as NGAL and KIM-1 are the most consistent markers, particularly for detecting complications such as acute kidney injury (AKI). Presepsin and serum lactate levels were the most reliable biomarkers for estimating the risk of septic shock and in-hospital mortality in urosepsis.

In summary, the reviewed studies agree that sepsis of abdominal origin requires a multimodal approach to biomarker interpretation. Inflammatory biomarkers, such as IL-18 and cytokine profiles, may help differentiate the infectious source; however, further validation is required as part of the combined panels. Similarly, emerging markers such as Pancreatic Stone Protein (PSP) show promising potential for improving risk stratification, although their practical implementation still depends on robust multicenter studies. Finally, the evidence supports that classical biomarkers, such as C-reactive protein (CRP) and procalcitonin (PCT), remain relevant; however, their utility in isolation is limited and significantly enhanced when used together and interpreted in the context of clinical progression and microbiological findings.

Furthermore, regarding the biomarker YKL-40 is a non-enzymatic protein released during inflammatory processes. It is primarily produced by neutrophils and macrophages and is involved in inflammation, tissue repair, and endothelial damage. Its blood levels increase during severe infections, and current data suggest that YKL- 40 could serve as a complementary marker for monitoring the severity of necrotizing soft tissue infections (NSTI). The lactate-to-albumin ratio appears to be a simple prognostic indicator applicable from the moment of arrival in the emergency department. However, the lack of solid and validated studies limits the integration of these biomarkers into routine clinical practice. Future studies should focus on the validation of combined panels and their integration with clinical scoring systems to optimize the management of patients with sepsis of skin and soft tissue origin.

The findings of this scoping review highlight the diversity of biomarkers used for the diagnosis and prognosis of sepsis and the differences in their reporting frequency depending on the infectious source. Nevertheless, significant knowledge gaps remain, particularly regarding the validation of emerging and omics-based biomarkers that could enhance diagnostic accuracy and risk stratification.

Future research should focus on several strategic lines aimed at strengthening the clinical applicability of biomarkers in sepsis. First, it is essential to conduct multicenter and prospective studies that robustly assess the clinical utility of both classical and emerging biomarkers and compare them across heterogeneous populations with different infectious focuses. Additionally, it is necessary to advance the integration of omics approaches, namely genomics, transcriptomics, proteomics, and metabolomics, together with traditional biomarkers, in order to explore combined profiles that enhance diagnostic sensitivity and specificity.

Similarly, the development of predictive models that incorporate biomarkers alongside clinical variables is encouraged, as this could optimize decision-making in critical care settings. Moreover, subgroup analyses based on the infection site are a priority because biomarker expression and performance can vary significantly depending on the origin of the infection. Finally, there is a strong need to promote research in local contexts and in regions with limited data, with the aim of ensuring that biomarker implementation is appropriate and tailored to diverse clinical settings.

This scoping review also identified limitations related to funding disclosures among the included studies. Five studies (31.2%) either did not report their funding sources or explicitly stated that no financial support was received. This lack of transparency restricts the ability to assess potential funding-related biases in the available evidence. Additionally, most funded research relies on governmental or academic support, with minimal industry participation, which may limit the development and evaluation of innovative biomarker-based technologies that are often driven by commercial investment. Furthermore, a clear geographical imbalance was observed, with most publicly funded studies originating from high- and middle-income countries. This may affect the representativeness of the evidence and hinder the identification of sepsis biomarkers that are particularly relevant in low-resource settings. Therefore, greater diversity in funding sources and improved reporting practices are needed to ensure equity, reduce publication bias, and support the global advancement of biomarker research on sepsis.

In conclusion, this scoping review demonstrates that the diagnostic and prognostic utility of biomarkers in sepsis varies according to the infection site. In pulmonary sepsis, presepsin and sFLT-1 are promising markers, whereas plasma gelsolin, transcriptomic profiles, and mNGS complement risk stratification. In urinary sepsis, NLR, PLR, NGAL, and KIM-1 are notable for the diagnosis and detection of complications, such as AKI, whereas presepsin and lactate retain their prognostic value. In intra-abdominal infections, IL-18 and PSP emerge as complementary tools, while CRP and PCT remain useful when used in combination. In skin and soft tissue infections, YKL-40 and the lactate/albumin ratio show potential, although the evidence remains limited. Overall, no biomarker should be interpreted in isolation; further multicenter research is needed to validate combined panels and omics-based approaches to enhance diagnostic and prognostic precision in the comprehensive management of sepsis.

Ethical considerations

Protection of persons. This study is a scoping review based exclusively on previously published data. No direct involvement of human participants was required; therefore, no risk to individuals was posed.

Protection of vulnerable populations. No vulnerable populations were directly involved in this study. All data were obtained from published literature, and no primary data collection was conducted.

Confidentiality. The study used only publicly available data from previously published articles. No identifiable personal information was accessed or handled.

Privacy. As this research did not involve direct interaction with participants or access to personal records, issues related to individual privacy were not applicable.

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Statement on the use of artificial intelligence.
No artificial intelligence (AI) tools were used in the writing, analysis, or preparation of this manuscript. All content was developed exclusively by the authors.

Authors´ contribution. LT conceived and designed the methodological approach and conducted the database search. VL and RA carried out the investigation, study selection, data extraction, and drafted and edited the manuscript. All authors contributed to read and approved the version of the submitted manuscript.

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