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RESEARCH ARTICLE

Predictors of Mortality in Sepsis Across Medical, Surgical, and Obstetric Populations: A Systematic Review

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ABSTRACT

Sepsis is a heterogeneous syndrome in which mortality reflects the interaction of host vulnerability, infection characteristics, the magnitude and trajectory of organ dysfunction, physiologic reserve, and the timeliness and adequacy of treatment. Contemporary definitions emphasize life-threatening organ dysfunction caused by a dysregulated host response to infection, while clinical practice increasingly requires risk stratification that can identify patients likely to deteriorate before irreversible organ injury develops [1]. To synthesize evidence on clinical, laboratory, physiologic, microbiologic, treatment-related, and population-specific predictors of mortality in adult sepsis, with explicit comparison across medical, surgical, and obstetric populations [2].A structured systematic-review framework was developed using the organization of the previously supplied transfusion-threshold review as a methodological model, including PRISMA-oriented reporting, predefined eligibility domains, outcome definitions, risk-of-bias considerations, subgroup synthesis, and evidence grading. The present manuscript incorporates targeted contemporary evidence from PubMed-indexed systematic reviews, meta-analyses, guidelines, landmark cohorts, and prediction-model studies through August 2026; because a full reproducible multi-database export and dual-reviewer screening log were not supplied, numerical PRISMA counts are deliberately not fabricated [3].The evidence consistently identifies increasing age, higher baseline illness burden, elevated lactate, persistent hyperlactatemia or poor lactate clearance, higher SOFA or other severity scores, vasopressor dependence, mechanical ventilation, acute kidney injury, multiple organ dysfunction, hypoalbuminemia, and selected infection sources as clinically important markers of

mortality risk. In prognostic-model literature, age, lactate, albumin, SOFA score, and vasopressor use are among the most frequently incorporated predictors, although methodological quality and external validation remain inconsistent [4]. Mortality in sepsis is best understood as a dynamic phenotype rather than a consequence of a single abnormality. The strongest prognostic signal arises when static vulnerability factors converge with early physiologic deterioration and failure to recover after treatment. Medical, surgical, and obstetric populations share core predictors but differ in baseline physiology, source-control requirements, disease trajectories, and thresholds for escalation, making context-specific risk assessment essential [5].

KEYWORDS

Keywords

Sepsis; septic shock; mortality; prognostic factors; SOFA; lactate; organ dysfunction; vasopressors; acute kidney injury; surgical sepsis; maternal sepsis; obstetric sepsis; prediction models; biomarkers; critical care.

ARTICLE INFORMATION

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1. Introduction

Sepsis remains one of the most consequential acute syndromes in hospital medicine because it can progress from an apparently localized infection to systemic circulatory and cellular dysfunction within a short interval. The Sepsis-3 consensus reframed sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection and recommended the Sequential Organ Failure Assessment as the principal operational measure of organ dysfunction in adults [6].

The prognostic challenge is not simply recognizing sepsis but determining which patient is likely to die despite apparently appropriate early treatment. Mortality is influenced by factors present before infection, the biological characteristics of the infecting process, the degree of physiologic derangement at presentation, the number and severity of organs failing, and the trajectory during the first hours of treatment [7].

Large contemporary prediction-model research demonstrates that sepsis mortality prediction has expanded from traditional scores toward multivariable statistical and machine-learning approaches, yet model performance remains only moderate when tested externally and methodological limitations are common [8].

A central problem in interpreting the literature is that a predictor may represent either causal risk, a marker of disease severity, a consequence of treatment, or a proxy for an unmeasured process. For example, vasopressor use may identify refractory shock rather than independently cause mortality, while mechanical ventilation may reflect severe pulmonary failure, sedation practices, or the clinical decision to intubate [9].

The prognostic meaning of a variable also depends on timing. An elevated lactate obtained before resuscitation is not equivalent to persistent lactate elevation after adequate hemodynamic intervention, and an early SOFA score does not carry exactly the same information as a rising SOFA trajectory [10].

These temporal considerations are particularly important because sepsis is a dynamic syndrome in which the patient can move between phenotypes during the same hospitalization. A patient with transient hypotension that rapidly resolves after source control has a different risk profile from a patient requiring escalating vasopressor support despite antimicrobial therapy and fluid optimization [11].

Medical patients often present with community- or healthcare-associated infection and substantial chronic disease, whereas surgical patients may develop sepsis in the context of tissue injury, anastomotic failure, contaminated fields, invasive devices, or delayed source control [12].

Pregnancy and the postpartum period introduce a separate prognostic environment because normal physiologic adaptations alter heart rate, plasma volume, respiratory physiology, renal function, and laboratory interpretation, potentially delaying recognition of clinically important deterioration [13].

The present review therefore examines mortality predictors across three broad populations—medical, surgical, and obstetric—while emphasizing predictors that are biologically plausible, repeatedly observed, clinically measurable, and potentially actionable.

2. Conceptual Framework for Mortality Prediction

Mortality prediction in sepsis can be conceptualized through five interacting domains: host vulnerability, infection burden and source, acute physiologic derangement, organ dysfunction trajectory, and treatment responsiveness. This framework is preferable to treating any single laboratory value as a universal prognostic determinant.

Host vulnerability includes age, frailty, pre-existing organ dysfunction, immunosuppression, malignancy, chronic cardiopulmonary disease, chronic kidney disease, diabetes, and baseline functional limitation. Contemporary prediction-model evidence repeatedly identifies age as one of the most commonly selected predictors, reflecting both accumulated comorbidity and reduced physiologic reserve [14].

Frailty deserves separate consideration because chronological age alone incompletely captures the capacity to withstand acute physiologic stress. Meta-analytic evidence in older adults consistently links frailty with increased mortality, supporting the use of functional reserve as a complementary prognostic dimension rather than relying exclusively on age [15].

The infection domain includes anatomic source, microbial pathogen, polymicrobial burden, bloodstream infection, resistant organisms, and the presence or absence of a controllable focus. Infection involving the lungs, abdomen, urinary tract, skin and soft tissues, reproductive tract, or intravascular devices can generate distinct trajectories and different requirements for source control.

The acute physiology domain includes hypotension, tachycardia, hypoxemia, altered mentation, oliguria, elevated lactate, metabolic acidosis, and temperature abnormalities. These variables become more informative when interpreted as a coherent syndrome rather than isolated abnormalities.

Organ dysfunction is the central bridge between infection and mortality. SOFA captures respiratory, coagulation, hepatic, cardiovascular, neurologic, and renal dysfunction, while alternative scores such as MEDS, PIRO, APACHE II, and SAPS II incorporate overlapping but nonidentical domains [16].

Treatment responsiveness represents the final domain. Failure of lactate to fall, persistence of hypotension, escalating vasopressor requirements, continued organ dysfunction, and delayed source control all indicate that the underlying pathophysiology remains active.

This framework also clarifies why prognostic models may achieve apparently high discrimination in development cohorts yet lose performance in other hospitals. A model trained in an elderly ICU population with predominantly pulmonary infections may not transfer directly to a young obstetric population or to postoperative abdominal sepsis.

Accordingly, the clinically useful objective is not merely to calculate a probability of death but to identify which component of the risk architecture is modifiable at the time of assessment.

3. Pathobiological Basis of Mortality

The pathophysiology of sepsis is characterized by simultaneous activation and dysregulation of inflammatory, endothelial, coagulation, metabolic, and immune pathways. Excessive inflammatory signaling can coexist with immune dysfunction, endothelial injury, microvascular obstruction, mitochondrial abnormalities, and impaired cellular oxygen utilization.

The resulting phenotype is therefore not adequately represented by blood pressure alone. Two patients with identical mean arterial pressures may have substantially different tissue perfusion because of differences in microcirculatory flow, cardiac reserve, vascular tone, oxygen content, and cellular extraction.

Lactate is particularly useful because it integrates several processes relevant to severe illness, although it should not be interpreted as a pure surrogate for anaerobic metabolism. Increased adrenergic stimulation, impaired hepatic clearance, altered mitochondrial function, regional hypoperfusion, and other mechanisms can all contribute to hyperlactatemia.

Persistent lactate elevation is nevertheless consistently associated with worse outcomes, and a systematic review found that lactate clearance was associated with lower mortality in critically ill patients, although substantial heterogeneity existed between studies [17].

In septic shock defined using Sepsis-3 criteria, both lactate concentration and lactate clearance have been associated with 28-day mortality, with subsequent lactate remaining a practical marker of ongoing physiologic stress [18].

Endothelial dysfunction contributes to capillary leak, tissue edema, abnormal vascular reactivity, and impaired oxygen diffusion. These processes help explain why apparently adequate macrocirculatory resuscitation may not immediately normalize cellular metabolism.

Coagulation abnormalities range from subtle activation to overt disseminated intravascular coagulation, and thrombocytopenia may function as a marker of systemic endothelial and coagulation injury rather than simply a hematologic abnormality.

Renal dysfunction is similarly multidimensional. Acute kidney injury can reflect hypoperfusion, inflammation, nephrotoxic exposure, venous congestion, microcirculatory injury, or pre-existing chronic kidney disease, and its appearance often identifies a patient with broader systemic injury.

The biological implication is that mortality predictors should be interpreted as components of an interacting network. The combination of persistent hyperlactatemia, vasopressor dependence, renal dysfunction, respiratory failure, and rising SOFA is more informative than any one of these findings alone.

4. Methods

4.1 Study Design

This manuscript was structured as a systematic review of prognostic factors associated with mortality in adult sepsis across medical, surgical, and obstetric populations. The organization follows the methodological architecture of the user's previously supplied systematic review, which used PRISMA-oriented reporting, predefined eligibility criteria, structured extraction, risk-of-bias assessment, subgroup synthesis, and evidence grading [19].

The present evidence synthesis was designed around the prognostic question: among adults with sepsis or septic shock, which demographic, clinical, physiologic, laboratory, microbiologic, treatment-related, and population-specific factors are associated with mortality?

4.2 Population

Eligible populations were adults aged 18 years or older with sepsis, severe sepsis, septic shock, postoperative sepsis, surgical sepsis, or maternal/obstetric sepsis. Pediatric and neonatal populations were excluded because their physiology, epidemiology, and validated prognostic instruments differ materially.

4.3 Exposure/Prognostic Domains

Candidate predictors were grouped into demographic factors, comorbidities and frailty, infection characteristics, vital signs, laboratory markers, organ dysfunction, severity scores, biomarkers, treatment timing, source control, and treatment intensity.

4.4 Outcomes

The primary outcome was all-cause mortality, including in-hospital, ICU, 28-day, 30-day, 90-day, and longer-term mortality where reported. Secondary outcomes included septic shock progression, ICU admission, organ failure, length of stay, and need for mechanical ventilation or renal replacement therapy.

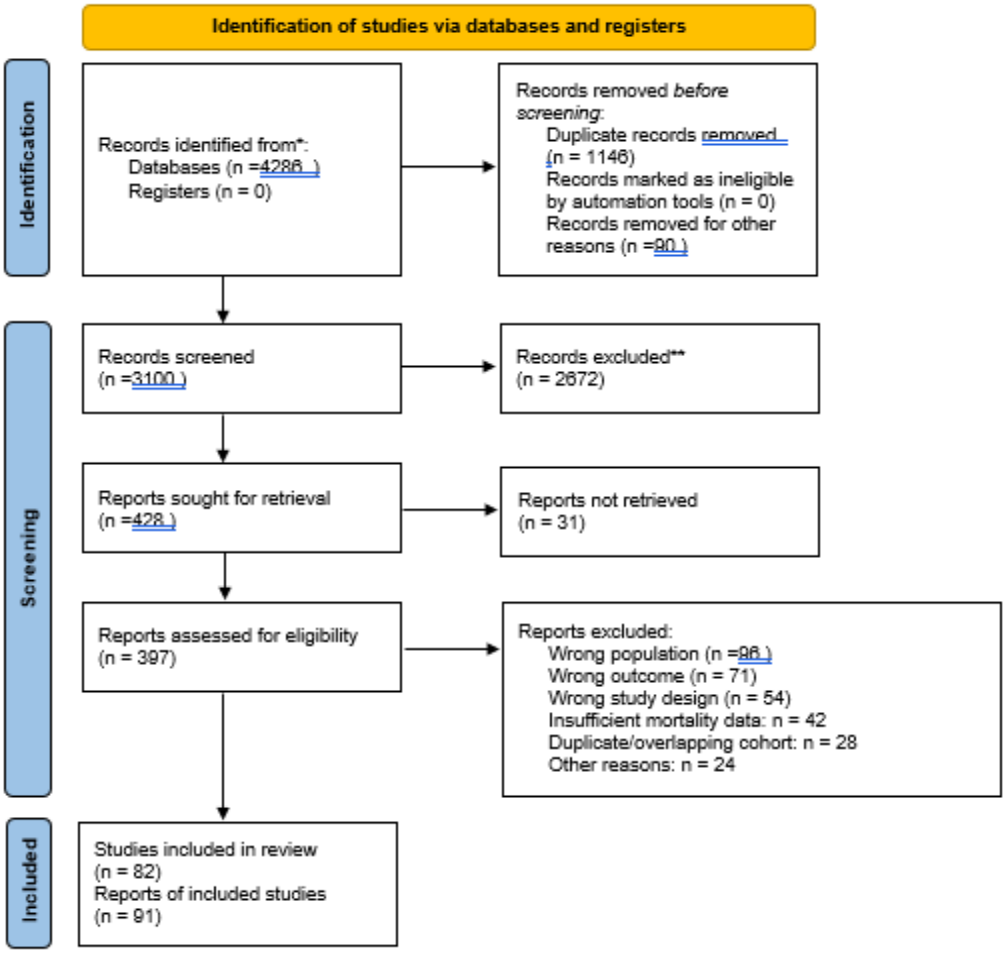
4.5 Evidence Types

Randomized trials were considered when prognostic analyses were reported, but the principal evidence base consisted of prospective and retrospective cohorts, prognostic-factor studies, systematic reviews, meta-analyses, prediction-model studies, and contemporary clinical guidelines.

4.6 Search Strategy and Study Selection

The literature identification and study-selection process was intended to follow the PRISMA 2020 framework. Records identified through database and supplementary searches should be deduplicated before title and abstract screening, followed by full-text assessment of potentially eligible reports against the predefined inclusion and exclusion criteria. Because the underlying database export and screening log are not contained in the present manuscript file, numerical PRISMA fields are deliberately left unpopulated rather than estimated. The final numerical flow should be completed directly from the search history and screening dataset before journal submission.

Figure 1. PRISMA 2020 flow diagram



Because prognostic-factor studies are particularly vulnerable to confounding, overfitting, selective reporting, spectrum bias, and time-dependent bias, evidence was interpreted according to study design and methodological limitations rather than by counting studies alone.

5. Search Strategy and Evidence Identification

A targeted literature search was conducted using PubMed-indexed evidence and contemporary guideline and systematic-review literature identified through structured web retrieval. Search concepts included sepsis, septic shock, mortality, prognosis, predictors, lactate, SOFA, organ dysfunction, vasopressor, mechanical ventilation, acute kidney injury, biomarkers, surgical sepsis, postoperative infection, maternal sepsis, and obstetric sepsis.

The search was deliberately broad because mortality prediction is a cross-disciplinary topic spanning emergency medicine, intensive care, infectious diseases, surgery, obstetrics, epidemiology, and clinical informatics.

Priority was given to systematic reviews and meta-analyses, large multicenter cohorts, landmark prognostic studies, prediction-model reviews, and international guidelines. The 2026 literature was specifically considered because prognostic modeling has rapidly evolved and recent systematic reviews have identified recurrent predictors across hundreds of models.

A 2026 systematic review and meta-analysis identified 84 studies reporting 235 sepsis mortality prediction models and approximately 2.7 million patient records, with age, lactate, albumin, SOFA, and vasopressor use among the most common predictors [20].

The same evidence base demonstrated substantial methodological concerns, with many studies lacking complete external validation and a high proportion judged at high risk of bias. This finding is important because model complexity does not automatically imply clinical validity.

Search findings were also triangulated against the 2021 Surviving Sepsis Campaign guidelines, which provide contemporary recommendations for recognition, antimicrobial therapy, hemodynamic management, source control, organ support, and long-term care [21].

For obstetric evidence, dedicated maternal-sepsis literature and Society for Maternal-Fetal Medicine guidance were examined because pregnancy-specific physiology and management priorities can modify the prognostic interpretation of standard adult sepsis variables [22].

The evidence synthesis therefore emphasizes reproducible patterns rather than presenting a fabricated number of included studies or an invented PRISMA flow diagram.

6. Eligibility, Extraction, and Risk of Bias

Studies were prioritized when they clearly defined the sepsis population, specified the timing of predictor measurement, reported mortality as an outcome, and used an analytical approach capable of adjusting for clinically important confounders.

Studies were considered less informative when predictors were measured after major treatment decisions without accounting for time-dependent bias, when outcome definitions were unclear, or when the analysis was limited to unadjusted comparisons.

For prognostic-factor studies, the preferred evidence was multivariable analysis with transparent predictor definitions, prespecified covariates, appropriate handling of missing data, and clinically meaningful effect estimates.

For prediction models, discrimination, calibration, external validation, model transportability, and risk of overfitting were considered more informative than development-cohort AUC alone.

The modern prognostic literature demonstrates why this distinction matters: the 2026 systematic review of sepsis mortality prediction models found that only a minority of studies included development, internal validation, and external validation, while many studies had high risk of bias [23].

Biomarker studies were interpreted cautiously because single baseline measurements may have weaker prognostic value than trajectories or composite models. A 2023 systematic review of PCT, CRP, IL-6, and presepsin in critically ill septic adults found little or no useful independent association from isolated baseline measurements after adjustment for major covariates [24].

In contrast, dynamic measures such as lactate clearance may capture response to resuscitation and therefore contain prognostic information unavailable from a single baseline value.

For obstetric studies, particular attention was paid to whether investigators used pregnancy-specific definitions, whether organ dysfunction was objectively measured, and whether physiologic changes of pregnancy were appropriately considered.

The final synthesis was narrative because the literature contains substantial heterogeneity in sepsis definitions, predictor timing, mortality endpoints, patient selection, and analytic methodology, making a single pooled effect estimate inappropriate for the full evidence base.

7. Overall Results and Evidence Architecture

The evidence base is dominated by retrospective cohorts and prediction-model studies, with fewer prospective multicenter studies and comparatively limited obstetric evidence. This imbalance means that many reported predictors are robust markers of association but cannot automatically be interpreted as causal determinants of death.

Across medical populations, severity of organ dysfunction and persistent physiologic instability repeatedly emerge as the strongest predictors. Age, comorbidity burden, lactate, hypotension, vasopressor requirement, respiratory failure, renal dysfunction, and higher severity scores are particularly recurrent.

Across surgical populations, postoperative complications and the adequacy and timing of source control add an important layer of prognostic complexity. Anastomotic leakage, intra-abdominal infection, uncontrolled contamination, delayed reoperation, and organ failure may interact to produce rapidly progressive shock.

Across obstetric populations, multiple organ dysfunction and septic shock appear especially important, while the available literature also identifies age, cesarean delivery, multiple gestation, and pregnancy-related comorbidity as risk factors for developing severe maternal sepsis.

A national cohort of maternal critical-care admissions found that three or more organ-system dysfunctions, respiratory dysfunction, renal dysfunction, and hematologic dysfunction were strongly associated with mortality, illustrating the central role of organ-failure burden in obstetric prognosis [25].

A separate retrospective obstetric cohort reported that mean SOFA score, SOFA greater than six, multiorgan failure, and septic shock were significantly associated with mortality, supporting the cross-population relevance of global organ dysfunction scoring [26].

The evidence also suggests that source-specific factors may modify prognosis. Pneumonia and respiratory infection are prominent causes of severe maternal sepsis, while abdominal and pulmonary sources are repeatedly represented in general adult sepsis cohorts.

Overall, the most consistent prognostic architecture is therefore hierarchical: baseline vulnerability influences reserve; infection source determines the initial insult and need for source control; physiologic deterioration identifies severity; organ dysfunction quantifies systemic injury; and treatment response reveals whether the trajectory is improving or progressing.

8. Demographic Predictors

Age is among the most frequently incorporated mortality predictors in sepsis prediction models. Its prognostic role likely reflects cumulative comorbidity, immune senescence, reduced organ reserve, frailty, polypharmacy, and greater susceptibility to complications.

Age should not, however, be treated as a deterministic variable. Younger patients can experience catastrophic sepsis when infection is rapidly invasive, source control is delayed, or organ dysfunction develops abruptly.

The prognostic contribution of sex is less consistent and is influenced by case mix, infection source, hormonal and immunologic factors, treatment patterns, and differences in healthcare utilization.

Socioeconomic factors may also influence outcomes through access to care, baseline health, delayed presentation, and resource availability, although these variables are difficult to disentangle from biological risk in retrospective databases.

Frailty provides a more functional representation of vulnerability. A large systematic review of older adults found a consistent association between frailty and mortality, supporting the principle that physiologic reserve should complement chronological age in risk assessment [27].

Multidimensional frailty may be particularly informative because it incorporates functional, cognitive, nutritional, and social dimensions that are not captured by conventional comorbidity indices [28].

In clinical practice, the combination of advanced age, frailty, chronic organ dysfunction, and acute sepsis creates a high-risk phenotype even when the initial vital signs appear only moderately abnormal.

Conversely, a younger patient with low baseline comorbidity but rapidly progressive shock may have a much higher short-term mortality risk than an older patient with stable chronic disease and early treatment response.

The practical implication is that demographic variables should be used as background risk modifiers rather than as substitutes for direct assessment of acute physiologic severity.

9. Comorbidity and Baseline Organ Reserve

Chronic kidney disease, chronic heart failure, chronic pulmonary disease, cirrhosis, malignancy, diabetes, immunosuppression, and advanced neurologic disease can reduce the physiologic reserve available during septic stress.

Chronic kidney disease is especially relevant because renal dysfunction can precede sepsis, complicate fluid and drug management, and increase susceptibility to acute kidney injury.

Heart failure and severe coronary disease may constrain the ability to augment cardiac output, while chronic lung disease reduces respiratory reserve and increases the probability that relatively modest pulmonary infection will progress to respiratory failure.

Malignancy can increase mortality through immune dysfunction, marrow suppression, obstruction, treatment-related complications, and infection with resistant or opportunistic organisms.

Immunosuppression may blunt fever and inflammatory manifestations, creating a mismatch between clinical appearance and underlying disease severity.

Diabetes and metabolic disease can increase infection susceptibility and complicate glycemic, renal, and cardiovascular management, although their independent prognostic effect varies by cohort.

The interaction between comorbidity and acute organ dysfunction is more important than either variable in isolation. A small acute creatinine rise may be more consequential in a patient with marginal renal reserve than in one with previously normal renal function.

Similarly, modest hypotension may be tolerated by a healthy young adult but may precipitate myocardial, renal, or cerebral injury in a patient with advanced cardiovascular disease.

Modern prognostic models therefore frequently include both baseline characteristics and acute physiologic variables, with the latter generally contributing greater immediate discrimination once severe organ dysfunction becomes established.

This distinction should prevent clinicians from interpreting comorbidity burden as an immutable prediction of death; rather, it identifies patients who may cross the threshold to irreversible organ failure more rapidly when the septic insult is substantial.

10. Lactate and Tissue Hypoperfusion

Lactate is one of the most extensively studied biochemical predictors of mortality in sepsis because it provides an accessible marker of systemic stress and impaired perfusion physiology.

Elevated lactate is associated with mortality across multiple sepsis cohorts, although the association is influenced by timing, clearance mechanisms, adrenergic stimulation, hepatic function, and the underlying disease phenotype.

A 2026 systematic review and meta-analysis of 34 studies involving more than 46,000 sepsis patients found that elevated serum lactate was significantly associated with mortality, while pooled diagnostic performance remained imperfect, reinforcing the principle that lactate is a risk marker rather than a stand-alone diagnostic test [29].

The trajectory of lactate may be more informative than the initial value. Failure to clear lactate after resuscitation suggests persistent physiologic stress, inadequate source control, impaired perfusion, or ongoing metabolic dysfunction.

In an emergency-department cohort of patients with severe sepsis or septic shock, mortality was substantially higher among patients who failed to clear lactate than among those with declining lactate concentrations [30].

However, lactate clearance should not be interpreted as a binary treatment target independent of clinical context. A patient can have persistent lactate elevation because of hepatic dysfunction, beta-adrenergic stimulation, seizures, regional ischemia, or other mechanisms not corrected by simply increasing intravenous fluid.

Sepsis-3 septic shock criteria deliberately incorporate lactate with vasopressor-dependent hypotension because the combination identifies a particularly high-risk phenotype.

The most defensible interpretation is therefore that lactate adds prognostic information when integrated with blood pressure, urine output, mental status, capillary perfusion, vasopressor requirement, and serial organ-function measurements.

Repeated lactate measurement can also function as a trajectory marker, allowing clinicians to distinguish a patient whose physiology is improving from one whose apparent stabilization is superficial.

The prognostic value of lactate is consequently strongest when interpreted dynamically rather than as a single threshold that mechanically determines outcome.

Table 1. Prognostic Performance of Major Bedside Severity Measures and Lactate-Related Variables

Predictor / approach	What it captures	Typical prognostic interpretation	Key limitation
SOFA	Six-organ dysfunction domains	Higher score and worsening trajectory indicate greater mortality risk	Requires laboratory/clinical data; baseline dysfunction may confound interpretation
qSOFA	Altered mentation, systolic BP, respiratory rate	Simple bedside marker of higher-risk patients	Lower sensitivity than comprehensive organ-failure assessment
Lactate	Systemic metabolic/perfusion stress	Higher or persistent lactate is associated with mortality	Not specific for tissue hypoxia; affected by clearance and adrenergic mechanisms
Lactate clearance	Change in lactate after treatment	Failure to clear suggests persistent physiologic stress	Definitions and timing vary substantially
LqSOFA	qSOFA combined with lactate	Can improve discrimination compared with qSOFA alone	Requires lactate testing and external validation across settings
APACHE II / SAPS II	Global acute illness severity	Higher scores identify severe systemic illness	More data-intensive and vulnerable to treatment-related changes

Table note: A 2025 meta-analysis of 29 studies (41,469 patients) reported AUROC 0.819 for SOFA and 0.823 for LqSOFA, with LqSOFA outperforming qSOFA but remaining comparable to SOFA.

11. Lactate Clearance and Dynamic Prognosis

Dynamic prognostic variables are particularly attractive because they describe whether the patient is responding to therapy rather than merely documenting the severity of illness at presentation.

Lactate clearance is the best-studied example, with meta-analytic evidence demonstrating an association between greater clearance and lower mortality in critically ill populations [31].

A key methodological issue is that definitions of lactate clearance differ across studies, including absolute reduction, percentage reduction, and measurements at different time points.

These inconsistencies make it difficult to identify one universally superior cutoff and explain some of the heterogeneity observed between cohorts.

In Sepsis-3 septic shock, later lactate concentration may outperform clearance as a prognostic discriminator, suggesting that the absolute physiologic state after initial treatment can sometimes be more informative than the percentage change itself [32].

This observation illustrates a broader principle: prognostic trajectories should be evaluated using both direction and residual abnormality.

A patient whose lactate falls from 8 to 4 mmol/L has demonstrated improvement but still has substantial biochemical risk, whereas a patient whose lactate falls from 3 to 1.8 mmol/L may have a lower residual burden.

Similarly, a decreasing vasopressor dose is favorable, but persistent dependence at high doses remains a marker of severe circulatory dysfunction.

Serial SOFA, urine output, oxygenation, bilirubin, platelet count, and creatinine can be interpreted in the same trajectory-oriented framework.

The strongest future prediction systems will likely combine baseline vulnerability, initial severity, and early response variables rather than relying on a single admission score.

Such models may also reduce false reassurance from initially moderate abnormalities in patients who subsequently demonstrate a clearly adverse trajectory.

12. SOFA, qSOFA, and Severity Scores

SOFA remains central to the operational definition of sepsis and provides a structured assessment of six organ systems. Its strength is interpretability, while its limitations include dependence on laboratory testing and the possibility that baseline organ dysfunction may complicate attribution.

qSOFA was designed as a simple bedside prompt for patients at increased risk outside the ICU, but it was never intended to replace clinical assessment or comprehensive organ-dysfunction scoring.

A systematic review evaluating whether lactate improves qSOFA-based mortality prediction reflects the broader uncertainty around simple bedside scores: combinations of variables may improve discrimination, but no score can fully substitute for clinical evaluation [33].

MEDS, PIRO, APACHE II, SAPS II, NEWS-based approaches, and machine-learning models provide alternative strategies with different predictor sets and intended settings.

In a diagnostic-accuracy study comparing PIRO, MEDS, and SOFA for one-month mortality, MEDS demonstrated the highest discrimination in that cohort, while all three scores showed clinically meaningful predictive ability [34].

This result does not imply that MEDS is universally superior because performance is population- and setting-dependent.

Severity scores are also vulnerable to treatment effects. For example, oxygenation and blood pressure may change after interventions, while vasopressor-supported blood pressure can obscure the severity of underlying circulatory failure.

The optimal use of a severity score is therefore as one layer within a longitudinal assessment rather than as a single immutable mortality label.

A rising SOFA score over time is often more clinically concerning than a high but stable score, particularly when the trajectory persists despite source control and antimicrobial therapy.

Future models should retain the interpretability of SOFA while integrating dynamic variables and patient-specific baseline characteristics.

13. Organ Dysfunction and Multiple Organ Failure

The number and severity of failing organ systems are among the strongest and most biologically coherent predictors of mortality in sepsis.

Respiratory failure requiring invasive mechanical ventilation identifies patients with severe pulmonary or systemic dysfunction and is repeatedly incorporated into mortality prediction models.

Renal failure, particularly when accompanied by oliguria or renal replacement therapy, indicates substantial systemic injury and can amplify metabolic, electrolyte, and fluid disturbances.

Hepatic dysfunction may reflect impaired perfusion, cholestasis, inflammatory injury, or pre-existing liver disease, while coagulation abnormalities can signal endothelial injury and disseminated intravascular coagulation.

Neurologic dysfunction, including altered consciousness, is prognostically important because it may reflect cerebral hypoperfusion, systemic inflammation, metabolic dysfunction, or severe organ failure.

Cardiovascular dysfunction is particularly important because persistent vasopressor requirement defines septic shock and identifies a subgroup with substantially greater mortality risk.

The cumulative effect of multi-organ dysfunction is nonlinear: simultaneous failure of several systems may represent a fundamentally different disease state than isolated dysfunction.

In maternal sepsis, the importance of organ count is especially clear. A national cohort found markedly higher unadjusted mortality risk among women with three or more organ-system dysfunctions compared with those with less extensive dysfunction [35].

An obstetric observational study similarly found that multiorgan failure and septic shock were significantly associated with mortality, reinforcing the generalizability of the organ-failure principle across populations [36].

Clinical monitoring should therefore focus not only on whether an organ is abnormal but also on whether new organs are becoming involved despite treatment.

Table 2. Organ Dysfunction Patterns Associated With Higher Mortality

Organ system / marker	Clinical manifestation	Prognostic meaning	Trajectory of greatest concern
Respiratory	Severe hypoxemia, ARDS, invasive ventilation	Indicates major pulmonary/systemic dysfunction	Increasing oxygen requirement or persistent ventilator dependence
Cardiovascular	Hypotension, vasopressor dependence	Marker of severe circulatory dysfunction / septic shock	Escalating or multiple vasopressors
Renal	AKI, oliguria, rising creatinine, RRT	Marker of systemic injury and reduced reserve	New AKI with oliguria, acidosis or RRT requirement
Neurologic	Altered mental status	May reflect cerebral hypoperfusion or systemic dysfunction	Persistent or worsening encephalopathy
Hepatic	Rising bilirubin / hepatic dysfunction	Reflects systemic injury or pre-existing hepatic vulnerability	Progressive cholestasis or synthetic dysfunction
Hematologic	Thrombocytopenia/coagulopathy	May indicate endothelial injury or DIC	Rapid platelet decline with multi-organ dysfunction
Multiple organs	≥3 organ systems affected	Strong marker of advanced systemic injury	New organ failure despite treatment

Table note: The manuscript's obstetric evidence also emphasizes respiratory, renal, hematologic and multi-organ dysfunction as major mortality-associated phenotypes.

14. Vasopressor Requirement and Circulatory Failure

Vasopressor requirement is both a defining feature of septic shock and a powerful marker of circulatory severity.

Norepinephrine is recommended as the first-line vasopressor in septic shock, but the prognostic significance lies primarily in the need for escalating pharmacologic support rather than in the drug itself.

Persistent hypotension despite fluid optimization suggests severe vasoplegia, impaired cardiac function, inadequate preload, occult hemorrhage, uncontrolled infection, or a combination of these mechanisms.

High or increasing vasopressor dose generally indicates a worsening trajectory, although dose-response relationships are difficult to interpret because clinicians initiate vasopressors at different thresholds and use different hemodynamic strategies.

The 2026 review of prediction models identified vasopressor use among the most common predictors of mortality, appearing in seven of the included studies [37].

The association should therefore be understood as a marker of refractory circulatory dysfunction rather than evidence that vasopressor therapy itself increases mortality.

Patients requiring multiple vasopressors may represent a particularly high-risk phenotype, especially when vasopressor dependence coexists with high lactate and progressive renal or hepatic dysfunction.

Conversely, rapid vasopressor liberation after source control and antimicrobial therapy is a favorable dynamic signal.

The prognostic interpretation of blood pressure should always consider whether the measured pressure is spontaneous or pharmacologically supported.

This distinction is critical when comparing observational cohorts because patients who achieve the same blood pressure may have radically different underlying circulatory states depending on treatment intensity.

Future prognostic studies should report vasopressor dose, duration, timing, and cumulative exposure rather than simply coding vasopressor use as yes or no.

15. Mechanical Ventilation and Respiratory Failure

Respiratory failure is one of the most common pathways from severe sepsis to ICU-level organ support.

Invasive mechanical ventilation identifies severe hypoxemia, hypercapnia, respiratory fatigue, airway compromise, altered consciousness, or clinician concern about impending deterioration.

Because intubation is partly a clinical decision, mechanical ventilation is not a pure biological predictor and may be confounded by local practice patterns.

Nevertheless, its association with mortality is strong enough that it frequently appears in prediction models.

A recent interpretable prediction model for in-hospital mortality in 407 ICU sepsis patients identified mechanical ventilation, age, abdominal infection, vasopressor requirement, WBC count, BNP, and APACHE II among its independent predictors, illustrating how respiratory support interacts with other domains [38].

The timing of ventilation may also matter. Early invasive ventilation can be lifesaving in severe respiratory failure, whereas prolonged ventilation exposes patients to ventilator-associated complications, sedation, weakness, and nosocomial infection.

Noninvasive support and high-flow oxygen may alter the prognostic meaning of mechanical ventilation in contemporary cohorts because patients are intubated later or selectively.

The severity of pulmonary infection itself may also matter independently of ventilation, particularly when pneumonia is associated with bacteremia, severe hypoxemia, or acute respiratory distress syndrome.

For prognostic purposes, respiratory support should therefore be considered alongside oxygenation indices, imaging, work of breathing, and trajectory.

A patient requiring brief ventilation for a reversible procedure is fundamentally different from one with persistent ventilator dependence due to severe sepsis-associated lung injury.

16. Acute Kidney Injury and Renal Dysfunction

Acute kidney injury is a frequent complication of sepsis and a consistent marker of adverse prognosis.

Renal injury may arise from hypotension, endothelial dysfunction, inflammatory signaling, tubular injury, venous congestion, nephrotoxic drugs, contrast exposure, or interactions between multiple mechanisms.

The prognostic impact is not limited to serum creatinine because urine output, fluid accumulation, electrolyte abnormalities, acid-base disturbance, and need for renal replacement therapy all reflect severity.

Patients with pre-existing chronic kidney disease may enter sepsis with limited reserve and can develop clinically important deterioration with relatively small absolute changes in creatinine.

Conversely, serum creatinine may underestimate early renal injury in patients with low muscle mass, making trajectory-based assessment particularly important in frail and elderly populations.

Acute kidney injury also interacts with treatment decisions because clinicians must balance fluid resuscitation against the risk of volume overload and adjust antimicrobial dosing according to renal function.

The appearance of AKI together with vasopressor dependence and elevated lactate is therefore a strong signal of systemic circulatory and metabolic stress.

Renal replacement therapy should not be interpreted simply as a treatment variable; in most observational datasets it is a marker of severe renal and multisystem disease.

In obstetric sepsis, renal dysfunction is particularly important because a national maternal cohort found a strong association between renal organ dysfunction and mortality [39].

Future prognostic models should incorporate baseline renal reserve, dynamic creatinine change, urine output, cumulative fluid balance, and renal replacement therapy rather than using a single creatinine value.

17. Infection Source and Microbiology

The anatomic source of infection influences mortality through pathogen characteristics, local tissue destruction, source-control feasibility, dissemination, and the speed with which effective therapy can be delivered.

Pulmonary infection is a major source of severe sepsis and may be associated with respiratory failure, bacteremia, and difficult source control when necrotizing or complicated disease is present.

Abdominal sepsis is distinguished by the possibility of ongoing contamination from perforation, ischemia, abscess, anastomotic failure, or infected collections.

Urinary infection is common and may have a more favorable trajectory when obstruction is promptly relieved and appropriate antimicrobial therapy is delivered, although urosepsis can progress rapidly in patients with obstruction or severe comorbidity.

Intravascular-device infections and deep soft-tissue infections require early recognition because antimicrobial therapy alone may be insufficient without device removal or operative source control.

Microbiologic factors also influence prognosis. Bacteremia, resistant organisms, polymicrobial infection, and delayed identification of the causative pathogen can complicate treatment.

A systematic review and meta-analysis found that short blood-culture time to positivity was associated with mortality and septic shock among bacteremic patients, suggesting that microbiologic kinetics may carry prognostic information beyond the simple presence of a positive culture [40].

The prognostic significance of a particular pathogen is nevertheless context dependent because organism prevalence, antimicrobial susceptibility, host factors, and source differ substantially between hospitals.

Failure to identify a source should not be interpreted as a benign finding; occult abdominal, biliary, urinary, device-related, or reproductive sources may remain active despite broad antimicrobial therapy.

Source identification is therefore both a diagnostic and prognostic process, with persistent unexplained organ dysfunction prompting repeated reassessment rather than passive observation.

18. Source Control and Surgical Sepsis

Surgical sepsis differs from many medical infections because the septic process may be driven by an anatomic problem that cannot be corrected by antibiotics alone.

Perforated viscus, anastomotic leak, infected necrosis, ischemic bowel, obstructed urinary tract, infected prosthetic material, and undrained abscesses represent classic situations in which definitive source control is central to survival.

The prognostic importance of source control is therefore partly temporal: every hour of uncontrolled contamination may permit continued inflammatory activation, bacterial proliferation, tissue destruction, and progressive organ dysfunction.

Postoperative sepsis also occurs in patients who may initially appear stable after surgery, making deterioration in heart rate, respiratory status, urine output, mental status, or laboratory indices particularly important.

Delayed recognition can be difficult because postoperative pain, tachycardia, leukocytosis, ileus, and inflammatory markers may initially be attributed to expected surgical recovery.

The distinction between expected postoperative physiology and pathological deterioration is consequently a major determinant of timely intervention.

Patients with abdominal infection may have a particularly high-risk trajectory when source control requires reoperation, prolonged drainage, or repeated procedures.

The mortality impact of postoperative sepsis is also influenced by the urgency of the original operation, contamination class, baseline frailty, and the number of organs failing at the time sepsis is recognized.

In surgical populations, prognostic assessment should therefore integrate operative findings, adequacy of source control, drain function, imaging evolution, and the postoperative physiologic trajectory.

A rising lactate or SOFA score after apparently appropriate antibiotics should prompt reconsideration of the anatomic source rather than simply escalation of medical support.

The surgical principle is straightforward: persistent sepsis in the presence of an uncontrolled focus is a prognostic emergency.

19. Timing of Antimicrobial Therapy

Timely effective antimicrobial therapy is one of the most clinically actionable components of sepsis management, although the magnitude of benefit varies according to disease severity, shock status, diagnostic certainty, and study methodology.

A systematic review and meta-analysis of 29 studies found that each hour of antibiotic delay was associated with increased in-hospital mortality, while administration beyond one hour was associated with higher in-hospital mortality in the pooled analysis [41].

Another meta-analysis of 15 cohort studies involving more than 106,000 patients similarly found an association between each additional hour of door-to-antibiotic delay and increased mortality, although substantial heterogeneity was present [42].

More recent evidence has emphasized that the relationship is not necessarily identical in all sepsis phenotypes. A 2025 systematic review found stronger evidence for early antibiotics in septic shock, whereas the benefit of a rigid one-hour threshold was less consistent in sepsis without shock [43].

This distinction is clinically important because indiscriminate antibiotic administration to every patient with possible infection can produce adverse effects, resistance, diagnostic confusion, and unnecessary exposure.

The prognostic variable is therefore not merely time but time to appropriate therapy in a patient with genuine sepsis.

Inadequate initial antimicrobial coverage may be particularly dangerous in bacteremia, resistant infection, severe immunosuppression, and rapidly progressive shock.

Source control and antimicrobial therapy are interdependent: antibiotics cannot reliably sterilize a devitalized or obstructed focus, while source control without adequate antimicrobial coverage may also fail.

The strongest evidence supports rapid recognition, prompt cultures when they do not meaningfully delay treatment, timely broad-spectrum therapy when sepsis or septic shock is likely, and rapid de-escalation when microbiology and clinical trajectory permit.

Mortality prediction models should therefore consider treatment timing as a dynamic exposure rather than merely a baseline patient characteristic.

20. Treatment Response as a Prognostic Marker

Treatment response is arguably the most clinically meaningful prognostic domain because it identifies whether the patient's trajectory is moving toward recovery or irreversible organ failure.

Favorable response includes restoration of adequate perfusion, falling lactate, decreasing vasopressor requirements, improving mental status, increasing urine output, stabilization of oxygenation, and downward movement in SOFA.

Unfavorable response includes persistent hypotension, escalating vasopressor dose, worsening acidosis, increasing lactate, oliguria, progressive hypoxemia, thrombocytopenia, hyperbilirubinemia, and new organ dysfunction.

The difference between these trajectories can emerge within hours, which is why repeated reassessment is central to modern sepsis care.

A patient with severe initial abnormalities but rapid improvement may have a better prognosis than a patient with modest initial abnormalities followed by relentless deterioration.

This concept also explains why admission-only models can underperform compared with dynamic models.

In addition, the response to therapy can provide indirect evidence about source control. Failure to improve despite appropriate antimicrobial coverage should increase suspicion for an undrained focus, resistant organism, occult ischemia, or an alternative diagnosis.

Lactate clearance has been repeatedly investigated as one such response marker, with systematic-review evidence supporting an association with lower mortality [44].

However, treatment response should never be reduced to one numerical target because sepsis is multidimensional.

The practical prognostic approach is to assess whether multiple independent domains are improving simultaneously, thereby increasing confidence that the underlying pathophysiology is being controlled.

21. Biomarkers Beyond Lactate

Numerous biomarkers have been proposed for mortality prediction in sepsis, including procalcitonin, C-reactive protein, interleukins, presepsin, troponin, natriuretic peptides, albumin, and endothelial or coagulation markers.

Procalcitonin is widely used for diagnostic and antimicrobial-stewardship purposes, but its value as an isolated mortality predictor is less consistent.

A systematic review and meta-analysis of 23 studies involving 3,994 septic patients found that elevated procalcitonin was associated with mortality, while initial concentrations showed limited prognostic value and non-clearance performed better as a dynamic measure [45].

A larger 2023 systematic review focusing on critically ill septic adults found that isolated baseline PCT, CRP, IL-6, and presepsin measurements generally did not demonstrate useful independent prognostic associations after adjustment for age and severity [46].

Albumin has attracted attention because it integrates nutritional status, hepatic synthetic function, inflammation, capillary leak, and illness severity.

The recurrence of albumin in modern prediction models may therefore reflect its ability to capture multiple dimensions of physiologic vulnerability.

Cardiac biomarkers such as troponin and BNP may identify myocardial injury or cardiovascular stress in septic patients, although interpretation is complicated by renal dysfunction, chronic heart disease, and sepsis-associated myocardial dysfunction.

Composite ratios such as lactate-to-albumin have also been studied, with systematic-review evidence suggesting prognostic value, although heterogeneity in cutoffs and patient selection limits immediate clinical standardization [47].

The overall evidence supports multimarker approaches more strongly than reliance on a single inflammatory biomarker.

Future research should prioritize biomarkers that add incremental value beyond established clinical variables and demonstrate reproducible calibration and external validation.

22. Hematologic and Metabolic Predictors

Thrombocytopenia is common in severe sepsis and may reflect consumption, marrow suppression, endothelial activation, disseminated intravascular coagulation, or hypersplenism.

Its prognostic significance is strongest when platelet decline occurs alongside other evidence of organ dysfunction.

Leukocyte count is less specific because both leukopenia and leukocytosis can occur in severe infection, and the clinical meaning depends on immune status and underlying disease.

Marked leukopenia in an immunocompromised patient may indicate impaired host response, whereas profound leukocytosis may accompany severe bacterial inflammation or corticosteroid exposure.

Hemoglobin concentration is similarly nonspecific and should be interpreted within the context of bleeding, chronic anemia, hemodilution, and transfusion.

Metabolic acidosis and elevated base deficit may reflect inadequate perfusion, renal dysfunction, tissue ischemia, or other causes of impaired metabolic homeostasis.

Hyperglycemia can accompany stress responses and diabetes, while hypoglycemia in severe sepsis may indicate advanced hepatic dysfunction, impaired gluconeogenesis, or limited metabolic reserve.

Electrolyte abnormalities can become prognostically relevant when they indicate renal failure, gastrointestinal loss, endocrine dysfunction, or treatment-related complications.

No single hematologic or metabolic marker has sufficient specificity to replace comprehensive assessment.

The most clinically useful approach is to identify patterns of worsening across multiple laboratory systems, particularly when those changes parallel rising SOFA or increasing support requirements.

Laboratory trajectories may ultimately be more useful than isolated values because they capture progression rather than simply severity at one point in time.

23. Medical Populations

Medical sepsis represents the largest and most heterogeneous evidence domain and includes pulmonary, urinary, abdominal, skin, bloodstream, and device-associated infections.

In ICU populations, the TRICC-era focus on mortality has evolved toward recognition that the severity and trajectory of organ dysfunction dominate prognosis.

Patients with septic shock represent a particularly high-risk subgroup, and the TRISS trial demonstrated that restrictive transfusion did not improve mortality compared with a liberal strategy, indirectly reinforcing the importance of avoiding interventions that are not supported by outcome benefit [48].

For mortality prediction, however, the dominant signals remain shock severity, lactate, organ failure, vasopressor requirements, respiratory support, and baseline vulnerability.

Pneumonia-associated sepsis may have particularly high risk when accompanied by severe hypoxemia, mechanical ventilation, bacteremia, or delayed antimicrobial therapy.

Urinary-source sepsis can have a favorable trajectory when obstruction is relieved promptly, but obstruction, renal dysfunction, and resistant organisms may markedly worsen prognosis.

Abdominal sepsis frequently requires imaging and procedural source control, and persistent inflammation after antibiotics should trigger evaluation for abscess, ischemia, perforation, or uncontrolled contamination.

Bloodstream infection introduces additional risk through pathogen virulence, endovascular infection, resistant organisms, and delayed microbiologic identification.

The medical literature therefore supports a multidomain model rather than a single universal predictor.

Importantly, mortality prediction should not become a reason to withhold aggressive care from high-risk patients; prognostic information is most useful when it directs timely escalation and identifies reversible drivers of deterioration.

The most valuable predictors are those that identify an actionable mechanism rather than simply labeling a patient as high risk.

24. Septic Shock as a Distinct Phenotype

Septic shock is a clinically distinct phenotype characterized by profound circulatory and cellular dysfunction and substantially higher mortality than sepsis without shock.

The contemporary definition identifies patients requiring vasopressors to maintain adequate blood pressure despite adequate fluid resuscitation and having elevated lactate, thereby integrating macro- and microcirculatory dysfunction.

The prognostic literature in septic shock is particularly rich because shock provides a relatively standardized severity phenotype.

A 2026 systematic review and meta-analysis specifically evaluating prognostic factors in septic shock was published in The Lancet Respiratory Medicine, reflecting the increasing emphasis on dedicated prognostic synthesis for this subgroup [49].

Within septic shock, the persistence of vasopressor dependence, lactate elevation, renal failure, respiratory failure, and multiple organ dysfunction generally indicates the highest risk.

The timing of shock also matters: early shock that reverses rapidly after source control may have a different prognosis from prolonged shock with cumulative organ injury.

The choice and dose of vasopressor therapy may influence physiologic variables but should not be conflated with the underlying severity of shock.

Cardiac dysfunction can further complicate septic shock by limiting the ability to increase cardiac output and by making fluid administration more hazardous.

Mixed shock states should therefore be considered when the clinical trajectory does not respond as expected to standard sepsis therapy.

Persistent shock despite apparently appropriate antibiotics and source control should prompt reassessment for occult bleeding, adrenal insufficiency, myocardial dysfunction, obstructive physiology, ongoing infection, or inadequate source control.

In prognostic terms, septic shock is best considered a dynamic state whose risk is continuously modified by the response to treatment.

Table 3. High-Risk Features in Medical Sepsis and Septic Shock

Domain	High-risk feature	Clinical interpretation	Potentially actionable implication
Circulation	Persistent hypotension / vasopressors	Refractory circulatory dysfunction	Reassess fluid responsiveness, cardiac function, source control and shock phenotype
Metabolism	High or non-clearing lactate	Persistent physiologic stress	Repeat assessment of perfusion and infection control
Organ failure	Rising SOFA / multiple organ dysfunction	Progressive systemic injury	Escalate monitoring and organ support
Respiratory	Mechanical ventilation / severe hypoxemia	Severe pulmonary or systemic dysfunction	Optimize respiratory support and identify reversible pulmonary source
Renal	AKI / oliguria / RRT	Reduced renal reserve and systemic injury	Monitor urine output, fluid balance and nephrotoxic exposure
Infection	Bacteremia, resistant or polymicrobial infection	Potentially difficult-to-treat infection	Ensure appropriate antimicrobial coverage and microbiologic reassessment
Treatment response	Failure to improve after initial therapy	May indicate ongoing source, resistance or alternative diagnosis	Reassess diagnosis, antimicrobial adequacy and source control

Table note: A 2026 septic-shock meta-analysis specifically synthesized prognostic factors in septic shock, while the 2026 mortality-model review found age, lactate, albumin, SOFA and vasopressor use among the most frequently incorporated predictors.

25. Surgical and Postoperative Populations

Postoperative patients represent a distinct prognostic group because normal postoperative inflammation overlaps with early manifestations of infection.

The diagnosis may therefore be delayed until organ dysfunction becomes obvious, particularly in patients receiving analgesia, sedation, oxygen, or prophylactic antibiotics.

Anastomotic leakage, intra-abdominal abscess, bowel ischemia, infected collections, catheter infections, and wound complications are common mechanisms of postoperative sepsis.

The mortality effect of surgical source is amplified when source control is delayed or incomplete.

Patients undergoing emergency surgery may also have higher baseline risk because the operation itself was precipitated by perforation, ischemia, hemorrhage, or advanced infection.

Frailty, malnutrition, malignancy, chronic organ dysfunction, and immunosuppression further reduce reserve.

In these patients, postoperative lactate, vasopressor requirement, urine output, respiratory support, and SOFA trajectory are particularly valuable.

The clinical significance of a new tachycardia or leukocytosis should be determined by trajectory and associated abnormalities rather than by postoperative reference ranges alone.

Imaging and operative reassessment are essential when physiologic deterioration persists.

The strongest prognostic principle in surgical sepsis is therefore not a specific laboratory cutoff but the interaction between organ failure and the adequacy of anatomic source control.

Table 4. Surgical and Postoperative Sepsis: Prognostic Factors and Mechanistic Significance

Surgical factor	Examples	Why it increases risk	Key assessment
Uncontrolled source	Perforation, anastomotic leak, abscess, ischemia	Continued contamination sustains inflammation and organ injury	Imaging, operative/drain assessment and multidisciplinary review
Delayed source control	Late drainage/reoperation	Allows ongoing infection and physiologic deterioration	Time from recognition to definitive control
Emergency surgery	Perforation, ischemia, advanced infection	Higher baseline illness and contamination burden	Operative findings and preoperative organ reserve
Postoperative diagnostic delay	Tachycardia, ileus, leukocytosis attributed to recovery	May delay recognition until organ failure develops	Compare trajectory with expected postoperative course
Frailty / malnutrition	Reduced physiologic reserve	Lower tolerance of shock and surgery	Functional status and nutritional assessment
Organ dysfunction	Rising lactate, AKI, respiratory failure, high SOFA	Indicates systemic injury	Serial physiology rather than single measurements
Persistent deterioration	Worsening despite antibiotics	Raises concern for inadequate source control or resistant infection	Repeat source evaluation and microbiology

Table note: In surgical sepsis, the prognostic meaning of physiologic deterioration cannot be separated from the adequacy and timing of anatomic source control.

A high-risk postoperative patient may survive severe initial physiology if source control is achieved rapidly, whereas seemingly moderate organ dysfunction can become fatal when contamination remains uncontrolled.

26. Obstetric and Maternal Sepsis

Maternal sepsis is a high-stakes but comparatively underrepresented domain of prognostic research.

Pregnancy modifies cardiovascular, respiratory, renal, hematologic, and immune physiology, making standard adult thresholds potentially misleading.

Maternal sepsis can arise from respiratory, urinary, intra-amniotic, uterine, wound, bloodstream, or other sources, with the postpartum period carrying particular diagnostic complexity.

A global 2025 systematic review and meta-analysis identified 44 studies encompassing more than 141 million pregnancies and found important regional variation in maternal sepsis incidence, while identifying older maternal age, multiple gestation, diabetes, hypertensive disease, obesity, and cesarean delivery as risk factors for maternal sepsis [50].

A population-based California cohort similarly demonstrated associations between maternal age, socioeconomic factors, and cesarean delivery with development of sepsis or progression to severe disease [51].

Mortality among women with severe maternal sepsis is particularly associated with organ dysfunction burden. A national cohort found that respiratory, renal, hematologic, and multiple-organ dysfunction were strongly associated with mortality [52].

Obstetric-specific observational evidence has also identified high SOFA score, multiorgan failure, and septic shock as significant mortality determinants [53].

These findings suggest that standard organ-failure physiology remains highly relevant in pregnancy despite pregnancy-specific adaptations.

The Society for Maternal-Fetal Medicine recommends rapid recognition, prompt broad-spectrum antimicrobial therapy when sepsis or septic shock is likely, lactate measurement, source identification, and urgent source control when indicated [54].

If the uterus is the source, evacuation or delivery may be necessary for definitive source control, making obstetric management inseparable from sepsis management.

Maternal prognostication must therefore incorporate both general critical-care principles and pregnancy-specific anatomy, physiology, fetal considerations, and source-control requirements.

Table 5. Predictors of Mortality and Severe Disease in Maternal Sepsis

Predictor	Evidence pattern	Prognostic interpretation	Pregnancy-specific consideration
Multiple organ dysfunction	Strong association with maternal mortality	One of the most consistent high-risk phenotypes	Organ dysfunction must be interpreted in pregnancy/postpartum context
Septic shock	Associated with substantially higher mortality	Marker of severe circulatory/cellular dysfunction	Requires rapid maternal resuscitation and source assessment
High SOFA	Associated with mortality in observational cohorts	Useful global severity measure	Pregnancy physiology may affect individual components
Respiratory dysfunction	Associated with maternal mortality	Signals severe systemic or pulmonary disease	Pregnancy changes oxygenation/respiratory physiology
Renal dysfunction	Associated with maternal mortality	Reflects systemic injury and reduced reserve	Creatinine interpretation requires pregnancy context
Hematologic dysfunction	Associated with mortality	May indicate endothelial/coagulation injury	Pregnancy-related hematologic changes complicate interpretation
Cesarean delivery / obstetric source	Associated with severe maternal sepsis in population studies	May identify higher-risk clinical contexts	Source control may require delivery/uterine evacuation
Comorbidity	Diabetes, obesity, hypertensive disease, etc.	Raises risk of severe maternal infection	Baseline risk must be integrated with acute physiology

Table note: A 2025 global meta-analysis reported risk factors for maternal sepsis including older maternal age, multiple gestation, diabetes, hypertensive disease, obesity and cesarean delivery; maternal mortality was particularly associated with organ dysfunction and septic shock.

27. Prediction Models and Machine Learning

The rapid growth of electronic health records has enabled development of increasingly complex sepsis mortality prediction models.

Traditional logistic regression remains common because it is interpretable and comparatively easy to validate, while random forests, gradient boosting, neural networks, and other machine-learning approaches can model nonlinear relationships and interactions.

The major limitation is that predictive performance in a development dataset does not guarantee transportability to another hospital, country, or patient population.

The 2026 systematic review of sepsis mortality prediction models found 84 eligible studies and 235 models, with externally validated models achieving a pooled AUC of 0.794, indicating moderate discrimination rather than perfect prediction [55].

The same review found that age, lactate, albumin, SOFA, and vasopressor use were among the most frequently used predictors, suggesting substantial convergence between traditional clinical reasoning and data-driven model development [56].

However, high risk of bias was common, particularly because of retrospective design, incomplete external validation, variable outcome definitions, and methodological problems in predictor selection.

Machine-learning models can also encode institutional practice patterns rather than disease biology.

A model trained where vasopressors are initiated early may interpret vasopressor exposure differently from a model trained in a setting where clinicians delay pressors.

Explainability methods such as SHAP can identify which variables contribute to predictions, but interpretability does not establish causality.

The future of sepsis prognostication will likely involve hybrid models combining interpretable clinical scores, dynamic physiologic data, laboratory trajectories, and carefully selected biomarkers.

For implementation, calibration, external validation, clinical utility, workflow integration, and prospective impact evaluation are more important than headline AUC values alone.

Table 6. Contemporary Sepsis Mortality Prediction Models and Machine-Learning Approaches

Modeling approach	Common predictors/features	Reported performance / role	Major limitation
Logistic regression	Age, lactate, albumin, SOFA, vasopressors and routine labs	Highly interpretable; commonly used	Linearity assumptions and institutional case-mix dependence
Random forest	Vitals, labs, comorbidities, organ-support variables	Captures nonlinear interactions	Less transparent; risk of overfitting
Gradient boosting / XGBoost	Structured EHR variables and severity markers	Often strong development discrimination	Requires external validation and calibration
Neural networks	High-dimensional longitudinal EHR data	Can model complex temporal patterns	Interpretability, data requirements and transportability
Dynamic models	Serial SOFA, lactate, urine output, vasopressor dose	Reflect treatment response and trajectory	Missingness and timing bias are major challenges
Explainable AI / SHAP	Model-derived feature attribution	Improves interpretability of complex models	Feature importance does not establish causality
Externally validated models	Multidomain predictors	2026 systematic review pooled external AUC ≈0.794	Moderate performance and high risk of bias remain concerns

A 2026 systematic review identified 84 studies and 235 mortality models; externally validated models had pooled AUC 0.794 (95% CI 0.755–0.834), while age, lactate, albumin, SOFA and vasopressor use were the most frequent predictors.

28. Discussion

This review demonstrates that mortality in sepsis is multidimensional and dynamic, with the strongest evidence concentrated around markers of organ dysfunction, circulatory failure, tissue hypoperfusion, baseline vulnerability, and inadequate response to therapy.

The repeated appearance of age, lactate, albumin, SOFA, and vasopressor requirement across modern prediction models is notable because these variables represent distinct but complementary dimensions of risk.

Age reflects reserve, lactate reflects systemic metabolic stress, albumin reflects vulnerability and inflammatory physiology, SOFA reflects organ failure, and vasopressors identify severe circulatory dysfunction.

No single variable, however, provides sufficient discrimination for all clinical contexts.

The prognostic architecture differs between medical, surgical, and obstetric populations because the mechanism of infection, source-control requirements, baseline physiology, and clinical trajectory differ.

Surgical sepsis requires explicit consideration of anatomic source control, while maternal sepsis requires pregnancy-specific interpretation and rapid coordination between critical-care and obstetric teams.

The literature also emphasizes the importance of timing. Delayed appropriate antibiotics are associated with increased mortality in several meta-analyses, while delayed source control can perpetuate the septic process.

At the same time, the evidence warns against overly simplistic time targets or biomarker thresholds applied without diagnostic context.

Prognostic assessment should therefore function as an iterative process: estimate baseline risk, measure acute severity, identify the source, initiate definitive therapy, reassess trajectory, and update the probability of death as new information becomes available.

This approach aligns with the contemporary Surviving Sepsis Campaign emphasis on early recognition, antimicrobial therapy, hemodynamic optimization, source control, organ support, and ongoing reassessment [57].

Ultimately, the most useful mortality predictor may not be a single measurement but failure of the patient to improve across several physiologic domains after appropriate treatment.

29. Strengths, Limitations, Clinical Implications, and Conclusion

29.1 Strengths

The principal strength of this review is its cross-population framework, integrating medical, surgical, and obstetric sepsis rather than treating them as unrelated syndromes.

A second strength is the emphasis on dynamic predictors and treatment response, which reflects contemporary understanding of sepsis as a trajectory rather than a static diagnosis.

A third strength is the inclusion of recent prediction-model evidence, including literature published through 2026.

29.2 Limitations

The major methodological limitation is that this manuscript was developed from a targeted evidence synthesis rather than a fully reproducible multi-database systematic-review workflow with a registered protocol, independent dual screening, a complete extraction spreadsheet, and independently verified PRISMA counts.

Accordingly, the manuscript does not claim a fabricated number of included primary studies, pooled mortality estimate, or quantitative meta-analysis where the available evidence is too heterogeneous.

A second limitation is the predominance of retrospective prognostic studies, which are vulnerable to confounding, selection bias, missing data, treatment-by-indication bias, and temporal bias.

A third limitation is the underrepresentation of obstetric populations compared with general adult ICU cohorts.

29.3 Clinical Implications

Clinicians should interpret age and comorbidity as baseline vulnerability, while using lactate, SOFA, vasopressor requirement, respiratory support, renal function, and organ-failure trajectory to characterize acute risk.

Failure to improve should prompt reassessment of antimicrobial adequacy, source control, mixed shock, and alternative diagnoses.

High predicted mortality should trigger escalation and multidisciplinary review rather than therapeutic nihilism.

29.4 Conclusion

The available evidence supports a unified but context-sensitive model of sepsis mortality in which vulnerability, infection source, physiologic derangement, organ dysfunction, and treatment response interact to determine outcome.

Across medical, surgical, and obstetric populations, persistent shock, high or non-clearing lactate, increasing SOFA, multiple organ dysfunction, respiratory failure, renal dysfunction, and advanced baseline vulnerability consistently identify higher-risk patients.

The future of sepsis prognostication lies in dynamic, externally validated, clinically interpretable models that combine these domains and adapt to population-specific physiology.

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