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Review

Multi-Omics and Artificial Intelligence in Adult Sepsis: From Risk Stratification to Organ-Dysfunction Prediction and Individualized Therapy

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Abstract: Sepsis encompasses biologically distinct host-response states, organ-injury pathways, and treatment susceptibilities despite similar clinical presentations, limiting population-level diagnostic, prognostic, and therapeutic strategies. This review examines how multi-omics and artificial intelligence can support four connected tasks in adult sepsis: molecular phenotyping, risk stratification, early prediction of organ dysfunction, and individualized treatment. Transcriptomic and single-cell studies provide the most mature frameworks for defining immune states, while spatial transcriptomics, proteomics, metabolomics, and integrated multi-omics add tissue, functional, and organ-specific information. Artificial intelligence can integrate these signals with electronic health records and monitoring data to assign phenotypes and update dynamic risk. However, prediction does not establish treatment benefit, and current evidence remains dominated by retrospective analyses, small or single-center cohorts, inconsistent sampling, dataset shift, limited external validation, and sparse randomized evidence for biomarker- or AI-guided interventions. Progress will require standardized longitudinal sampling, multicenter validation, calibrated and explainable models, and prospective trials testing whether model-guided decisions improve patient-centered outcomes.

Keywords: adult sepsis; multi-omics; artificial intelligence; organ dysfunction; precision medicine

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1. Introduction

1.1. Clinical Burden and Unmet Needs in Sepsis Management

Sepsis is a life-threatening syndrome in which a dysregulated host response to infection causes acute organ dysfunction, yet this syndromic definition encompasses diverse pathogens, host states, injury patterns, and trajectories [1,2]. Despite advances in recognition, antimicrobials, source control, resuscitation, and organ support, clinicians still cannot reliably determine who will deteriorate, which organ will fail next, or which intervention will provide net benefit at a given time [1,3].

Diagnostic and prognostic uncertainty emerge early. Culture optimization, multiplex polymerase chain reaction, novel methods of pathogen detection (e.g., T2 magnetic resonance), metagenomic sequencing, and rapid susceptibility platforms can accelerate microbiological information, but their effect depends on analytical coverage, distinction between colonization and infection, resistance data, and stewardship integration [4]. Likewise, conventional organ markers often identify established rather than impending injury, leaving an interval in which molecular deterioration may precede unequivocal clinical criteria [5,6]. Precision care therefore requires decision-specific tools that distinguish infection from clinically similar inflammation, identify coherent risk states, predict organ dysfunction with meaningful lead time, and determine whether treatment should differ between patients [1,7].

1.2. Sepsis Heterogeneity and the Need for Precision Medicine

The failure of therapies tested across unselected sepsis populations partly reflects biological incoherence: an average effect may conceal benefit in one subgroup, neutrality in another, and harm in a third [1,7]. A phenotype describes observable characteristics, a subphenotype a data-derived subgroup, and an endotype a subgroup linked to a distinct mechanism; only a subset becomes actionable when it also predicts a clinically relevant outcome or differential treatment response [1,2].

These states are not necessarily fixed. Hyperinflammation and immune suppression may coexist, and their relative contribution can change within a patient over time [2,8,9]. Multi-omics studies further resolve myeloid, interferon, mitochondrial, lipid, and adaptive-immune programs within apparently similar clinical presentations [10,11]. Yet molecular structure is not automatically reproducible or useful. In a prospective 43-hospital study of 1327 adults, omics-specific unsupervised clusters showed limited concordance, whereas goal-directed subgroup identification produced more reproducible scores linked to defined clinical strategies [12]. Phenotype discovery, prognostic prediction, and prediction of treatment benefit are therefore distinct inferential tasks [7,12]. The translational goal is instead a temporally anchored, externally reproducible tool that adds value to routine care and, for therapeutic claims, demonstrates credible biomarker-by-treatment interaction [7,13,14].

1.3. Convergence of Multi-Omics and Artificial Intelligence for Precision Sepsis Care

Multi-omics offers complementary views of heterogeneity. Bulk transcriptomics captures dynamic host-response programs, single-cell methods localize them to immune-cell states, and spatial transcriptomics places immune and parenchymal signals within tissue architecture [15–17]. Proteomics measures functional effectors and potentially deployable fluid biomarkers, whereas metabolomics reflects immune activation, mitochondrial stress, substrate use, organ clearance, nutrition, and treatment exposure [18–20]. Integration can connect regulation, cellular origin, functional pathways, and physiology only when modalities, patients, and sampling times are explicitly aligned (Figure 1) [7,12].

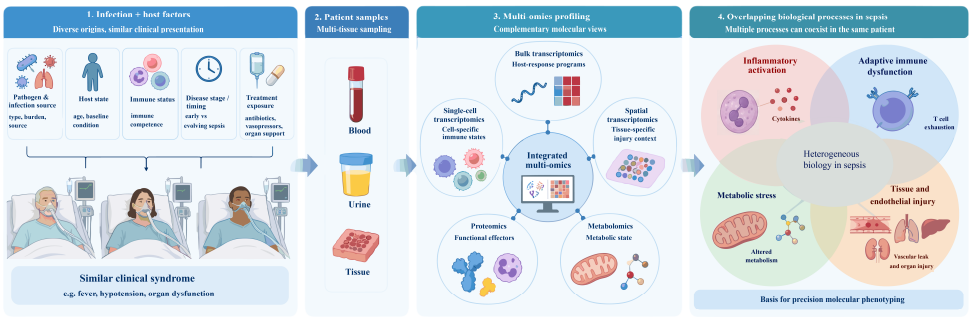


Figure 1. Multi-omics resolution of biological heterogeneity in adult sepsis.

Diverse pathogens, host characteristics, immune states, disease stages, and treatment exposures contribute to substantial biological heterogeneity despite apparently similar clinical presentations. Multi-tissue sampling

combined with bulk transcriptomics, single-cell transcriptomics, spatial transcriptomics, proteomics, and metabolomics captures complementary dimensions of host-response programs, cellular states, tissue context, functional effectors, and metabolic alterations. Integration across these molecular layers can resolve overlapping inflammatory, adaptive immune, metabolic, endothelial, and tissue-injury states, providing a biological basis for precision molecular phenotyping in sepsis.

Artificial intelligence provides the analytical bridge from high-dimensional measurement to patient-level inference. It can identify phenotypes, compress signatures into parsimonious panels, and integrate clinical and molecular variables, but it also introduces risks of overfitting, unstable feature selection, limited generalizability, and inadequate validation [13,21]. Organ dysfunction offers a concrete test: urinary extracellular-vesicle proteomics and blood transcriptomics have yielded candidate signals for early or persistent sepsis-associated acute kidney injury, whereas respiratory and cardiovascular studies remain largely mechanistic, retrospective, or underpowered [19,22–24]. The relevant endpoints are lead time, calibration, incremental utility, and whether a prediction can trigger a safe response [7,25].

The ultimate objective is individualized treatment, not more elaborate risk description. Multi-omics treatment-effect modeling has produced a transcriptomic score and six-protein surrogate for restrictive fluid therapy, but the estimated benefit remains observational [14]. Immune-guided therapy requires repeated state measurements, and computational drug candidates still require safety, biomarker selection, and randomized evaluation.

This review examines four linked tasks: molecular phenotyping, risk stratification, early organ-dysfunction prediction, and individualized treatment. Rather than cataloging omics platforms or artificial intelligence (AI) algorithms, we organize the evidence according to its proximity to clinical decision-making, distinguishing discovery, internal validation, external validation, prospective clinical evaluation, and evidence of treatment benefit. Across these tasks, we distinguish association, classification, prediction, causal inference, and clinical utility. The final section proposes a translational pathway based on temporally aligned multicenter data, deployable assays, external calibration, prospective impact evaluation, and treatment-interaction testing.

To identify relevant literature, PubMed and the Web of Science Core Collection were searched on 31 July 2026. No publication-date restriction was applied, and the retrieved records spanned 2008–2026. Controlled vocabulary and free-text terms related to sepsis, septic shock, or severe sepsis were combined with terms for multi-omics, integrative omics, pan-omics, and integrated or combined omics. The searches retrieved 650 records, of which 371 unique records remained after deduplication and were screened for relevance to the scope of this narrative review. Priority was given to adult human evidence, particularly original investigations with clinically relevant comparators, longitudinal or multicenter designs, external or prospective validation, and outcomes relevant to clinical decision-making. Pediatric, neonatal, and inseparable mixed-age studies were excluded from the core evidence base. Animal or *in vitro* studies were cited selectively when they provided important mechanistic or translational context and were not treated as evidence of clinical effectiveness in adults.

2. Multi-Omics for Deciphering Sepsis Heterogeneity

2.1. Transcriptomics and Single-Cell Approaches for Molecular Phenotyping

Among the available omics layers, bulk transcriptomics has provided one of the most extensively studied discovery frameworks for molecular phenotyping in adult sepsis because host ribonucleic acid (RNA) profiles respond rapidly to infection, immune activation, physiological stress, and treatment exposure. These profiles have been used to derive signatures for bacterial–viral discrimination, prognosis, and molecular endotyping, thereby revealing structure that is not captured by a syndromic diagnosis or a conventional severity score [15]. However, a transcriptomic signature is not intrinsically an endotype: its clinical meaning depends on the comparator, sampling time, platform, preprocessing pipeline, and whether the signal is reproducible in clinically similar rather than healthy control populations [15,26]. Batch effects and unstable feature selection can therefore transform an apparently strong discovery result into a poorly transportable assay [13,15].

Bulk measurements also conflate changes in circulating cell composition with transcriptional reprogramming within individual cells [16,27]. Comparator choice further determines the intended task: sepsis versus healthy controls measures broad illness-related separation, whereas sepsis versus sterile inflammation, infection without organ dysfunction, or other critical illness better tests diagnostic specificity [13,15]. A signature derived after treatment may also encode corticosteroids, antimicrobials, transfusion, or organ support rather than untreated host biology, making precise time anchoring essential [2,15]. Single-cell RNA sequencing addresses cellular ambiguity by resolving neutrophil maturation, monocyte and macrophage activation, lymphocyte exhaustion, and B-cell or plasma-cell remodeling within the same clinical syndrome [16,27]. Across adult datasets, recurrent patterns include emergency granulopoiesis, expansion of immature or suppressive myeloid states, reduced antigen-presentation programs, and

impaired cytotoxic function of T cells and natural killer (NK) cells. These patterns support a state-space model in which inflammatory amplification and adaptive immune suppression can coexist, rather than a rigid sequence of an early hyperinflammatory phase followed by a uniformly immunosuppressed phase [8,27].

Neutrophils illustrate why cell-resolved phenotyping matters [16,28]. Multi-omics and single-cell studies distinguish mature inflammatory, immature emergency-granulopoietic, metabolically adapted, and immunoregulatory neutrophil states whose relative abundance and transcriptional programs vary with disease stage and outcome [16,27]. Chitinase-1-positive neutrophils, for example, link a bulk prognostic signal to a candidate myeloid state characterized by concurrent inflammatory activation and reduced human leukocyte antigen-related expression, but the single-cell sample size, pseudotime ordering, and ligand–receptor analyses remain inferential [28]. Consequently, cell-state labels should be supported by patient-level replication, protein or functional measurements, and predefined clinical endpoints rather than by the number of sequenced cells [16,27].

The translational objective is therefore not to maximize the number of differential genes or cell clusters, but to compress reproducible biology into low-dimensional measurements that retain patient-level discrimination across platforms and centers [13,15]. A useful transcriptomic panel should be tested against clinically plausible comparators, locked before external validation, and evaluated for calibration, lead time, incremental value, and feasibility within the treatment window [7,15]. Single-cell analysis can identify the cellular origin and functional context of that panel, whereas deployment will usually require a smaller polymerase chain reaction (PCR), protein, flow-cytometric, or combined assay [8,16]. This division of labor moves molecular phenotyping from a discovery atlas toward a clinically testable classification system [2,15].

Single-cell multi-omics has begun to resolve dynamic immune heterogeneity in sepsis, including monocyte trajectories, CD8 T-cell dysfunction, and persistent immunosuppression, although these computationally inferred states remain unvalidated as a bedside "immune clock" [29]. Integration with genetic instruments has nominated candidate immune programs but provides limited causal evidence [30]. Prospective blood-genomic studies support reproducible adult sepsis endotypes [31]. Single-cell analyses may also generate pharmacodynamic hypotheses, as illustrated by treatment-associated immune shifts with ulinastatin, although observational designs cannot establish treatment effects [32].

2.2. Spatial Transcriptomics for Resolving Tissue-Specific Mechanisms of Organ Injury

Circulating RNA and protein measurements cannot by themselves determine whether a signal originates from immune cells, injured parenchyma, endothelium, or altered organ clearance [17,33]. Spatial transcriptomics addresses this limitation by anchoring gene-expression programs to anatomical regions and multicellular neighborhoods, thereby distinguishing a diffuse systemic response from localized tissue injury. Its principal value in sepsis is therefore not an additional molecular layer, but a bridge between blood-derived phenotypes and organ-specific mechanisms [17].

Sepsis-associated acute kidney injury currently provides the clearest spatially informed example, although the direct evidence remains predominantly preclinical. Integrative analyses of murine lipopolysaccharide and cecal ligation and puncture models suggest overlapping modules of endothelial instability, macrophage–endothelial regulation, regional leukocyte recruitment, tubular metabolic suppression, and repair. These models also produce different spatial and temporal patterns, indicating that "experimental sepsis" should not be treated as a single homogeneous exposure. Co-localization and inferred ligand–receptor pairs can prioritize mechanisms, but spot-level measurements mix cells and do not establish binding, directionality, or causal communication without orthogonal protein localization or perturbation [17].

Direct adult evidence remains limited: available kidney disease maps are mainly derived from small murine datasets, whereas human material is often anatomical reference tissue [17]. Adult sepsis-associated acute kidney injury (SA-AKI) spatial endotypes should therefore not be presented as established. The lung poses an analogous challenge in separating systemic inflammation from alveolar, endothelial, and myeloid injury; proposed lung–gut, lung–kidney, and lung–heart pathways remain predominantly preclinical or computational [24,34]. Future studies should integrate accessible biofluid biomarkers with tissue profiles when ethically available, preserve clinical event-time anchors, and determine whether localized molecular states precede organ dysfunction and yield deployable surrogates [17,19].

Complementary non-spatial transcriptomic and experimental studies also implicate ferroptosis and pyroptosis in tissue-specific injury. Hepatocyte peroxisome proliferator-activated receptor alpha (PPARα) activity has been linked to lipid peroxidation and ferroptotic liver injury, whereas gasdermin-D-mediated pyroptosis may amplify systemic inflammation and parenchymal damage [35,36]. Although these findings provide candidate mechanisms

for future spatial investigation, they remain predominantly preclinical and should not be interpreted as validated adult organ endotypes.

2.3. Proteomics and Metabolomics for Biomarker Discovery and Functional Characterization

Proteomics and metabolomics connect transcriptional states to functional effectors and physiological consequences [37,38]. Proteins offer direct access to inflammatory mediators, complement, coagulation, endothelial injury, extracellular vesicles, and post-translational regulation, whereas metabolites integrate substrate use, mitochondrial activity, redox balance, organ clearance, nutrition, microbiota, and drug exposure [33,38,39]. Their proximity to measurable clinical specimens makes both layers attractive for translating high-dimensional discovery into targeted panels [18,19].

Proteomic interpretation nevertheless depends strongly on specimen and measurement context. Whole-organ proteomics can identify pathways that are invisible to plasma assays, but it mixes cell abundance with intracellular regulation and may not indicate whether a candidate can be detected non-invasively. Phosphoproteomics adds regulatory information, yet a changed phosphosite may reflect altered modification stoichiometry, altered abundance of the parent protein, or technical missingness [39]. Urinary extracellular-vesicle proteomics offers a potential liquid-biopsy route: CD35-positive vesicles have been associated with established and subclinical SA-AKI, persistent injury, death, and acute kidney disease in adult cohorts. Even in this relatively strong example, the discovery sample was small, vesicle processing and urine dilution may affect thresholds, and the inferred podocyte origin requires further validation [19].

Metabolomics captures a particularly dynamic but highly confounded layer of sepsis biology [20,38]. Recurrent findings implicate glycolysis, oxidative phosphorylation, fatty-acid oxidation, amino-acid and tryptophan metabolism, glutathione balance, oxidized nicotinamide adenine dinucleotide (NAD+) metabolism, and mitochondrial danger signaling [20,33,37]. These pathways should be interpreted as context-dependent networks rather than as universally high or low metabolites, because the same concentration can reflect production, consumption, redistribution, renal or hepatic clearance, nutritional intake, or treatment [33,38]. Non-targeted metabolomics also faces uncertainty in metabolite identification, so discovery signals should be chemically confirmed and quantitatively validated before translation into clinical assays [18,37].

Protein–metabolite integration is most informative when both layers are measured in the same patients at aligned time points and interpreted against relevant clinical controls [18,37]. Integrated analyses can identify coordinated inflammatory-protein and amino-acid metabolic modules, but correlation alone does not establish biochemical regulation [37]. Translation therefore requires paired sampling, targeted validation, appropriate clinical metadata, analytical quality control, and external evaluation of a predefined low-dimensional panel [18,37].

Extracellular vesicles provide another bridge between cellular origin and circulating measurement. Multi-omic profiling of serum exosomes has shown that vesicle RNA, protein, and metabolite cargo changes across sepsis development, while cell-specific exosome studies in sepsis-associated acute respiratory distress syndrome (ARDS) propose links to immunometabolic reprogramming [40,41]. Pre-analytical isolation, cellular attribution, and normalization remain insufficiently standardized, so extracellular-vesicle signatures should be treated as candidate organ-proximal biomarkers rather than interchangeable plasma measurements.

Metabolic heterogeneity also extends beyond canonical glycolysis. Adult observational work has linked androgen status to illness severity without establishing benefit from hormone replacement, and experimental syntheses indicate that immunometabolic reprogramming contributes to multiple-organ dysfunction through coupled changes in substrate use, redox state, and mitochondrial function [42,43]. In sepsis-associated encephalopathy, reviews and small multi-omics cohorts implicate NAD+, tryptophan, glutathione, and microbiota-related pathways; cluster of differentiation 38-related signatures remain promising but require larger adult validation [44–46].

2.4. Multi-Omics Integration toward Precision Phenotyping

Multi-omics integration is clinically useful only when the integration strategy matches the biological question and the structure of the data. Early fusion combines normalized features before modeling, late fusion combines modality-specific predictions, intermediate or latent-factor methods learn shared representations, and network or pathway approaches incorporate prior biological structure [47]. No integration strategy is universally optimal; the appropriate choice depends on whether modalities are paired within the same patient, collected at aligned time points, affected by systematic missingness, or derived from different cohorts [7,48]. Analyzing transcriptomic and metabolomic datasets side by side is therefore not equivalent to estimating patient-level cross-omics relationships [37,48].

Longitudinal paired data can reveal whether a molecular state is stable, reversible, or associated with a changing outcome, but the term “longitudinal” requires scrutiny. In a study using biospecimens from the Reevaluation of

Systemic Early Neuromuscular Blockade (ROSE) trial, integration of transcriptomic and metabolomic data collected on days 0 and 2 identified both inflammatory-phenotype-specific and phenotype-independent factors associated with mortality, with directional replication in the Early Assessment of Renal and Lung Injury (EARLI) adult sepsis cohort. However, the two sampling time points were insufficient to resolve continuous trajectories, most latent factors showed limited temporal variation, and external validation relied primarily on feature-score projection rather than complete model retraining and clinical calibration [10]. Separate animals sampled at 0, 8, and 24 h are even more limited because treatment, time, and between-animal variation cannot be separated as within-subject change [18].

The most important methodological lesson comes from a prospective 43-hospital study of 1327 adults, in which unsupervised clustering performed separately on different omics layers produced poorly concordant patient subgroups. When subgroup identification was instead defined around a specific clinical strategy, the resulting scores were more reproducible, suggesting that clinically anchored stratification may be more useful than purely descriptive clustering. However, the apparent heterogeneity in treatment effect remained based on observational data and model estimates rather than biomarker-guided randomization [12]. Similarly, a transcriptomic treatment-benefit score and its six-protein surrogate identified adults with septic shock who appeared more likely to benefit from restrictive fluid therapy, but treatment was not assigned according to the biomarker and the mortality benefit was model-estimated [14]. Together, these studies illustrate a shift from describing biological heterogeneity to asking which patients may benefit from which treatment, while also showing that treatment-response phenotypes ultimately require prospective testing of biomarker-by-treatment interactions [12,14].

Recent integration studies illustrate both the potential and the limitations of precision phenotyping. Reviews of omics-based diagnostics emphasize that different analytical layers provide distinct types of information and should not be integrated without considering sampling time and specimen source [49]. Exploratory adult and public-data studies have linked glycolytic–immune programs, endosome–lysosome–autophagy dysregulation, and organ-specific molecular modules to candidate subtypes [50,51]. These signatures expand biological hypotheses, but many rely on retrospective datasets and require locked classifiers, clinically relevant controls, and independent validation before use.

Integration can also link systemic endotypes to clinically deployable organ-specific markers. In an adult SA-AKI cohort, combining a validated whole-blood transcriptomic endotype with protein biomarkers improved risk stratification for kidney replacement therapy or death, as well as for short-term mortality, with different biomarkers contributing across endotypes [52]. This design is clinically informative because it evaluates complementary, rather than merely correlated, modalities, although its value for treatment selection and prospective clinical utility remains unproven. Other studies have identified interleukin-1 receptor type 2 (IL-1R2)-related inflammatory signaling and dual-pathway small-molecule strategies as potential therapeutic targets, but these candidates are supported primarily by public-dataset integration and experimental models [53,54].

3. Artificial Intelligence for Risk Stratification and Outcome Prediction

3.1. AI-Based Identification of Sepsis Phenotypes

The molecular states described in Section 2 become clinically useful only if a new patient can be assigned to them reproducibly and within a clinically relevant decision window [7]. Artificial intelligence contributes at two distinct stages: unsupervised approaches can uncover latent molecular structures, whereas supervised classifiers aim to assign subsequent patients to predefined states [2]. Conflating these two tasks can make exploratory molecular patterns appear closer to clinical deployment than the evidence actually supports [12].

Unsupervised clustering, consensus clustering, latent-class analysis, matrix factorization, and network-based methods have been used to identify clinical subphenotypes, transcriptomic endotypes, immune-cell states, and multi-omics factors. The resulting molecular subtypes may be sensitive to feature selection, cohort composition, and analytical strategy, underscoring the need for independent validation of candidate clusters [55]. Accordingly, candidate clusters should be evaluated for resampling stability, replication in independent adult cohorts, biological coherence, temporal consistency, and relevance to a prespecified clinical task [12]. Candidate clusters derived from a limited set of molecular features require independent replication and orthogonal biological validation before they can be considered robust endotypes [56].

Once a discovery phenotype has been established, supervised assignment models may enable predefined states to be recognized in external cohorts without repeatedly redefining the phenotype [2]. Such models should quantify assignment uncertainty and accommodate dynamic state transitions rather than forcing every patient into a fixed category. Validation should compare new patients with a predefined reference framework, quantify assignment confidence, and determine whether the phenotype retains comparable biological and clinical meaning across centers [7]. This recognition step represents an essential translational bridge from exploratory clustering to clinically applicable stratification, which remains insufficiently implemented in many phenotyping studies.

Cell-resolved AI can link patient groups to specific immune states [16]. Single-cell co-expression analysis and machine-learning approaches have identified candidate neutrophil subsets and hub genes, but small and imbalanced donor cohorts, reliance on healthy-control comparisons, batch effects, and limited experimental validation constrain clinical interpretation [56]. The patient should remain the independent statistical unit, because randomly partitioning cells from the same donor between training and testing can introduce pseudoreplication and yield overly optimistic performance estimates. A deployable classifier must therefore translate cell-level discoveries into patient-level features that can be measured reproducibly in routinely collected clinical specimens [8].

AI-derived phenotypes may be defined using molecular data, routinely collected physiological data, or a combination of both. Multi-omics studies have identified mitochondrial oxidative-stress subtypes and digestive-system immune profiles, although their reproducibility may be limited by repeated use of public datasets and heterogeneity in feature spaces [57,58]. In contrast, deep learning applied to routinely collected adult electronic health record (EHR) data identified three SA-AKI subphenotypes with markedly different rates of dialysis use and 28-day mortality, demonstrating substantial clinical heterogeneity while leaving the underlying biological mechanisms unresolved [59]. Phenotypes derived from vital-sign trajectories have also undergone external evaluation and have been associated with differential treatment patterns, supporting the value of time-dependent classification over approaches based solely on admission data, although these associations do not establish differential treatment benefit [60].

3.2. AI Prediction of Mortality and Disease Progression

Electronic-health-record models offer rapidly available inputs and can establish a practical clinical baseline for risk prediction, but their labels and predictors are vulnerable to treatment leakage, documentation practices, and site-specific workflows [61]. When clinical predictive value is claimed, a molecular model should therefore be compared with a well-specified routine-care model rather than with no comparator. Its value should be judged by discrimination, calibration, lead time, and clinically meaningful incremental value or reclassification, rather than by statistical significance alone.

Transcriptomic machine-learning studies illustrate how performance changes with increasingly realistic validation. A 28-gene model achieved an area under the receiver operating characteristic curve (AUC) of 0.970 in an independent public dataset and 0.870 in a small validation cohort using quantitative reverse-transcription polymerase chain reaction (qRT-PCR), whereas a panel designed to distinguish sepsis from systemic inflammatory response syndrome (SIRS)—a more clinically challenging classification task—achieved an AUC of 0.745 in qRT-PCR testing. This gradient is informative because healthy or broadly dissimilar controls create easier separation than patients with competing inflammatory syndromes [13]. Public-dataset heterogeneity can support transport testing, but it also creates risks of hidden sample overlap, inconsistent preprocessing, and feature-selection leakage [13,25].

Other multi-omics models address mortality, coagulation, pathogen-specific biology, or metabolic–immune risk states. Models for sepsis-associated coagulopathy can identify candidate molecular heterogeneity, yet retrospective public datasets and circular feature selection limit the transfer of a coagulation subgroup to general sepsis prognosis [62]. Genome-wide association study and quantitative trait locus integration and machine learning have prioritized mitochondrial genes with pathogen-associated differences, but an internally cross-validated AUC cannot substitute for prospective testing in pathogen-confirmed adult cohorts [63]. Similarly, a five-gene metabolic score showed only moderate survival discrimination despite much stronger sepsis-versus-healthy separation, emphasizing that diagnosis and prognosis are different tasks [64].

Mortality prediction also differs from prediction of disease progression. A day-1 blood transcriptomic model distinguished persistent from transient SA-AKI more strongly than a clinical model in a study of 172 adults, but the held-out data came from the same study network and the worsening group contained only 10 patients [23]. In longitudinal transcriptomic–metabolomic work, mortality-associated factors could be projected into an independent adult sepsis cohort, yet only two time points were available and external paired multi-omics data were limited [10]. Trajectory models therefore require event-aligned repeated measurements, competing-risk handling, and outcomes such as recovery, persistent dysfunction, recurrence, or treatment escalation rather than a single terminal label.

As summarized in Table 1, recent biomarker and machine-learning studies have explored diverse molecular signatures, including combined biomarker panels, metabolic–immune features, genetic evidence, and candidate molecular markers [65–68]. However, reported performance often declines with more clinically realistic validation. Healthy-control comparisons and internal validation may overestimate clinical utility, and the clinical advantage of machine-learning models requires rigorous external and prospective validation [69]. Therefore, locked models require external validation, calibration, subgroup assessment, and demonstration of incremental clinical benefit, particularly given heterogeneity in populations, outcomes, and prediction horizons.

Table 1. Selected artificial intelligence and multi-omics studies across sepsis classification, risk stratification, and organ-dysfunction phenotyping and prediction.

Study	Clinical Outcome and Comparator	Adult Population or Data Source	Input Modalities	Model or Analytic Approach	Key Result	Validation Design	Main Limitation
Yang et al., 2026 [13]	Sepsis diagnosis comparing sepsis with non-sepsis controls and a separate sepsis-versus-SIRS evaluation	Eight public cohorts; 1166 samples; small qRT-PCR validation	Bulk transcriptomics + scRNA-seq + experimental readouts	SVM-RFE and logistic regression	External-dataset AUC 0.970 for the 28-gene panel; qRT-PCR AUC 0.870; sepsis–SIRS qRT-PCR AUC 0.745	Independent retrospective datasets plus a small qRT-PCR cohort no prospective evaluation	Dataset shift and possible leakage; no prospective clinical-impact study
Qian et al., 2026 [62]	Survival/mortality prediction within sepsis molecular subgroup comparison	Public and study-derived sepsis molecular datasets	Integrated multi-omics features	Machine-learning survival modeling	Generated molecular subgroups and a candidate survival model	Retrospective internal and external dataset evaluation no prospective evaluation	Potential batch effects and overfitting; clinical calibration and impact remain unproven
Jin et al., 2026 [63]	Pathogen-specific sepsis classification pathogen-defined subgroup comparison	Adult sepsis public multi-omics datasets	Mitochondrial and immune multi-omics features	Integrative machine learning and translational prioritization	Prioritized mitochondrial biomarkers for pathogen-specific sepsis classification	Retrospective cross-dataset computational validation no prospective pathogen-confirmed evaluation	Retrospective public-data analysis; requires prospective pathogen-confirmed validation
Alipanah-Lechner et al., 2026 [10]	Mortality-associated factors across inflammatory phenotypes survivors versus non-survivors	160 adults from the multicenter ROSE trial; independent EARLI adult sepsis cohort	Paired day-0/day-2 whole-blood transcriptomics + plasma metabolomics	MEFISTO latent-factor integration and feature-score projection	Identified phenotype-specific and shared mortality-associated immune-metabolic factors with directional replication in EARLI	Independent-cohort feature-score projection no full model retraining calibration or prospective impact evaluation	Only two time points; extreme phenotype sampling; external paired multi-omics n = 61; no calibration or clinical-impact evaluation
Huang et al., 2025 [18]	Concurrent SA-AKI discrimination SA-AKI versus non-SA-AKI	Single-center adult cohort, n = 56; linked mouse discovery study	Kidney proteomics + metabolomics followed by targeted serum metabolite measurement	Multi-omics biomarker selection and three-marker IC3 model	3-hydroxybutyrate, creatine, and inosine yielded a mean internal AUC of 0.90	Internal validation only repeated 70/30 splits no independent external or prospective validation	Concurrent discrimination rather than pre-AKI prediction; no external validation; small cohort with potential severity and renal-clearance confounding
Li et al., 2025 [19]	SA-AKI and subclinical AKI discrimination persistent versus non-persistent kidney dysfunction	Discovery 8 + 8; validation n = 134; prospective n = 72	Single urinary-EV proteomics + clinical outcomes	Candidate selection and ROC analysis	CD35-uEV AUC 0.89 for SA-AKI and 0.84 for subclinical AKI; associated with persistent AKI and AKD	Independent validation cohort plus prospective observational cohort no model-guided clinical-impact evaluation	Assay standardization, urine dilution, thresholds, incremental value, and decision impact remain unresolved
Zhang et al., 2022 [23]	SA-AKI trajectory classification persistent versus transient SA-AKI	172 adults: no AKI 50, persistent 62, transient 50, worsening 10	Day-1 peripheral-blood transcriptomics + clinical variables	Gene-feature SVM	Distinguished persistent from transient SA-AKI with held-out AUC 0.948 versus 0.739 for the clinical model	Same-network held-out validation no independent external or prospective validation	Only day-1 molecular sampling; SOFA-renal rather than full KDIGO trajectories; worsening group n = 10

Table 1. *Cont.*

Study	Clinical Outcome and Comparator	Adult Population or Data Source	Input Modalities	Model or Analytic Approach	Key Result	Validation Design	Main Limitation
Bollen Pinto et al., 2021 [22]	Myocardial injury/dysfunction phenotyping within septic shock	27 adults with septic shock	Clinical, echocardiographic, transcriptomic, proteomic, and metabolomic data (~58,600 features)	Stability-based exploratory machine-learning pipeline	Generated candidate features associated with myocardial injury and cardiac dysfunction	Exploratory analysis only no independent external or prospective validation	$p \gg$ n, few outcome events, substantial overfitting and selection-bias risk
Lambertucci et al., 2026 [70]	MODS severity and mortality association within sepsis human prognostic cohorts	Human discovery n = 43 and validation n = 424; three mouse sepsis models	Plasma DBI/ACBP + multi-organ transcriptomic, metabolic, and immune profiling	Clinical association plus experimental perturbation	DBI/ACBP correlated with severity and mortality; antibody neutralization improved survival and organ function in mice	Independent human observational validation plus multi-model animal experiments no prospective treatment evaluation	Human evidence is observational; therapeutic causality and safety derive from animals

Abbreviations: ACBP, acyl-CoA-binding protein; AKD, acute kidney disease; AKI, acute kidney injury; AUC, area under the receiver operating characteristic curve; CD35, cluster of differentiation 35; DBI, diazepam-binding inhibitor; EARLI, Early Assessment of Renal and Lung Injury; EV, extracellular vesicle; IC3, inosine–creatine–3-hydroxybutyrate model; KDIGO, Kidney Disease: Improving Global Outcomes; MEFISTO, Method for the Functional Integration of Spatial and Temporal Omics data; MODS, multiple organ dysfunction syndrome; qRT-PCR, quantitative reverse-transcription polymerase chain reaction; ROC, receiver operating characteristic; ROSE, Reevaluation of Systemic Early Neuromuscular Blockade; SA-AKI, sepsis-associated acute kidney injury; scRNA-seq, single-cell RNA sequencing; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; SVM, support vector machine; SVM-RFE, support vector machine-recursive feature elimination; uEV, urinary extracellular vesicle.

3.3. Multimodal AI Integrating Clinical and Molecular Data

Multimodal risk assessment aims to combine clinical history, laboratory data, omics, imaging, and continuous monitoring into a temporally coherent patient representation [21]. These inputs operate at different frequencies: molecular assays may be measured once or twice, imaging intermittently, and hemodynamic or waveform data continuously [7]. Integration must therefore preserve when each variable became available and whether it preceded the target event [25]. Missingness is itself informative when samples cannot be obtained because of early death, low urine output, transfusion, or limited specimen volume, so complete-case analysis may select a lower-risk or otherwise atypical population.

Routine laboratory biomarkers provide an important clinical bridge between omics discovery and deployable artificial intelligence. Procalcitonin (PCT), C-reactive protein (CRP), monocyte distribution width (MDW), and complete blood count (CBC)-derived indices are rapidly available, relatively inexpensive, and repeatable, although no single marker is sufficiently sensitive or specific to replace clinical assessment. MDW, a measure of monocyte size heterogeneity generated during automated CBC analysis, has been proposed for early sepsis screening, particularly in emergency-department and intensive-care settings [71]. In a multicenter study including 5344 patients from six cohorts, machine-learning models integrating MDW with CBC parameters achieved internal AUCs of 0.91–0.98 and external AUCs of 0.75–0.95 across emergency-department and intensive-care cohorts, outperforming single-biomarker baselines but still requiring prospective impact evaluation [72]. Their translational value should therefore be tested as incremental benefit beyond conventional clinical assessment and established markers such as PCT and CRP, using calibration, decision-curve analysis, and prospective workflow evaluation. Serial measurements may help capture changing inflammatory and hematological states and monitor progression or recovery; however, time-varying models must align sampling with treatment and outcome windows and determine whether repeated measurements improve prediction or management beyond admission values.

Small myocardial-injury studies demonstrate both the attraction and danger of multimodal modeling. In one cohort, approximately 58,600 clinical, echocardiographic, transcriptomic, proteomic, and metabolomic features were explored in only 27 adults with septic shock. Stability-based selection can generate hypotheses in such a $p \gg n$ setting, but it cannot overcome the limited number of patients and outcome events or provide credible external performance [22]. Molecular candidates such as nuclear factor interleukin 3 regulated may gain support from cross-species data, single-cell localization, genetic inference, and experiments, yet they remain unsuitable as clinical predictors without prospective adult cardiac phenotyping [73].

Validation should include modality-ablation experiments and a deployment simulation. Ablation shows whether omics, imaging, or monitoring adds information beyond the other modalities, while simulation determines whether the required data are available before the intended decision. A model whose accuracy collapses when one expensive molecular assay is missing may be scientifically informative but operationally fragile. The most concrete test of added value is early organ-dysfunction prediction linked to a safe and explicit clinical response [25].

Multimodal models should be evaluated against the best available single-modality baseline. Studies integrating microbiota, metabolites, immune signals, and machine learning have nominated gut-derived metabolic mechanisms in sepsis and mitochondrial immunometabolic networks in sepsis-associated encephalopathy [74,75]. These analyses broaden biological coverage but often combine datasets rather than contemporaneously paired modalities. Reviews of AI-enabled sepsis care similarly emphasize real-time monitoring and personalized support, while highlighting the need for further clinical validation and implementation evidence [69]. A multimodal claim should therefore require paired patient-level inputs, an ablation analysis showing incremental contribution, and calibration in an external clinical workflow.

4. AI-Enabled Prediction and Management of Sepsis-Associated Organ Dysfunction

4.1. Prediction of Acute Kidney Injury

SA-AKI is an instructive application because serum creatinine and urine output are essential clinical criteria but may lag biological injury or be modified by fluid balance, muscle mass, diuretics, and baseline renal function [76,77]. Prediction should be divided into at least four tasks: incident acute kidney injury (AKI) before diagnostic criteria are met, progression in severity, persistence versus recovery, and longer-term acute kidney disease or chronic sequelae [23,76]. Combining these endpoints into a single "AKI prediction" label obscures different time windows and clinical actions.

Urinary extracellular vesicles provide a more organ-proximal route. Following an 8 + 8 discovery stage, CD35-positive urinary vesicles were evaluated in a 134-person validation cohort and a 72-person prospective cohort, with reported AUCs of 0.89 for SA-AKI and 0.84 for subclinical AKI. The marker was also associated with persistent AKI, death, and acute kidney disease, offering a bridge between early injury and renal trajectory.

Nevertheless, urine dilution, vesicle isolation, assay thresholds, incremental value over conventional markers, and the inferred podocyte origin requires multicenter confirmation [19].

Blood transcriptomics offers a complementary trajectory signal. In 172 adults, a day-1 gene-feature support-vector machine distinguished persistent from transient SA-AKI with a held-out AUC of 0.948, compared with 0.739 for a clinical model, but the validation remained within the same study network. The model used renal trajectories defined by the Sequential Organ Failure Assessment (SOFA) score rather than the complete Kidney Disease: Improving Global Outcomes (KDIGO) criteria, and the small number of patients in the worsening subgroup limited the multi-state analysis [23]. A clinically useful successor should be tested at a landmark preceding the predicted transition and incorporate urine output and baseline kidney function [76]. Calibration should then be reported separately for each renal trajectory.

Metabolic panels further demonstrate why the time anchor matters. Three metabolites distinguished adults with diagnosed SA-AKI from sepsis without AKI in a 56-person cohort, but sampling occurred on the diagnostic day and repeated 70/30 splits did not constitute external validation. The signals may reflect renal clearance, global severity, nutrition, hepatic metabolism, or shock rather than a kidney-specific pre-injury process [18]. Thus, a high concurrent AUC should not be described as an advance warning.

Clinical decision support must connect risk to actions with plausible benefit and acceptable harm [78]. Candidate responses include reviewing nephrotoxins, optimizing hemodynamics without indiscriminate fluid loading, adjusting drug dosing, intensifying urine and creatinine monitoring, and evaluating indications for kidney support. A model should not independently trigger renal replacement therapy, because the timing and modality of kidney replacement therapy require the full clinical context and have not been validated as model-triggered interventions in these molecular studies [76].

Evaluation should compare prediction landmarks before and after routine clinical recognition [23]. A useful model must show how many hours of lead time it provides, how performance changes across baseline chronic kidney disease and shock severity, and whether the proposed action remains beneficial when the prediction is false. Renal recovery, dialysis-free survival, and longer-term kidney function should accompany incident AKI because prevention of a creatinine-defined event is not the only patient-centered objective [19,76]. Table 1 therefore places the three-metabolite model comprising inosine, creatine, and 3-hydroxybutyrate (IC3) at an exploratory stage, while CD35-positive urinary extracellular vesicle (CD35-uEV) and the transcriptomic trajectory model remain promising but not implementation-ready [18,19,23].

SA-AKI demonstrates why classification, prediction, and trajectory modeling should be separated. Deep-learning phenotyping identifies groups with different outcome burdens, whereas supervised models estimate incident AKI risk and require temporally valid external evaluation [59,79]. Early creatinine-trajectory modeling has identified eight adult classes with different risks of acute kidney disease and death, including external validation in a second intensive care unit (ICU) database [79]. These trajectory classes can improve prognostic description but do not establish that changing therapy according to class improves renal recovery.

Molecular layers may add biological specificity to these clinical trajectories. Reviews of SA-AKI multi-omics summarize transcriptomic, proteomic, metabolomic, and epigenetic candidates, while deoxyribonucleic acid methylation studies and experimental tubular-cell work implicate durable regulatory change and myeloid differentiation primary response 88-associated senescence [80–82]. The combined transcriptomic-endotype and protein-biomarker study provides a more direct adult example of incremental stratification [52]. Future models should test whether these measurements improve calibration and decision benefit beyond serial creatinine, urine output, hemodynamics, and treatment exposure.

4.2. Prediction of Respiratory Failure and Cardiovascular Dysfunction

For respiratory failure, a clinically useful model would combine gas exchange, ventilatory support, imaging, hemodynamics, and temporally aligned molecular markers [25]. Public-data analyses and animal studies implicate a signaling axis involving S100 calcium-binding protein A9 (S100A9), interleukin-17, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and caspase-3 in septic lung epithelial injury, but they do not establish a clinically validated predictor in adults or demonstrate that targeting S100A9 provides clinical benefit in humans [83]. Molecular measurements should therefore complement, not replace, continuous assessment of oxygenation, respiratory mechanics, and treatment exposure [7].

Cardiovascular prediction is complicated by inconsistent definitions of septic cardiomyopathy and by the load dependence of many echocardiographic measures [5]. Cardiac injury, ventricular dysfunction, vasoplegia, microcirculatory failure, and treatment effects can coexist without representing a single phenotype [5,84]. Strain

imaging, serial echocardiography, biomarkers, hemodynamics, and molecular data should therefore be interpreted as complementary views of a changing cardiovascular state [84,85].

Dynamic cardiopulmonary models should predict a defined transition, such as escalating oxygen or ventilatory support, worsening shock, new ventricular dysfunction, or rising vasopressor requirement [84]. They should also account for the intervention–measurement feedback loop, because fluids, vasopressors, ventilation, sedation, and renal support alter both physiology and molecular readouts [84,85].

Validation should be stratified by infection source, ventilation status, baseline cardiac disease, and the definition used for organ dysfunction [5,24]. A model trained on echocardiography obtained because clinicians suspected cardiac dysfunction may inherit referral bias and perform differently under systematic screening. Likewise, a respiratory model must distinguish prediction of ARDS onset from prediction of ventilation, because ventilation decisions depend on clinical practice as well as biology [25]. Table 1 highlights that current cardiopulmonary multi-omics evidence remains hypothesis-generating compared with the more advanced renal biomarker cohorts [19,22].

For respiratory dysfunction, multi-omics and machine-learning analyses have associated lactylation-related immune infiltration with sepsis-associated ARDS, and extracellular-vesicle reviews propose cell-specific immunometabolic signals [41,86]. These studies provide mechanistic candidates rather than validated forecasts of intubation, worsening oxygenation, or ventilator-free days. Equivalent cardiovascular programs will need serial echocardiography and hemodynamic data paired with molecular sampling, not merely cross-sectional discrimination between cases and controls.

4.3. Dynamic Prediction of Multiple Organ Dysfunction

Multiple organ dysfunction syndrome (MODS) is not simply a count of static organ endpoints; it is an evolving network in which immune mediators, endothelial injury, microcirculation, extracellular vesicles, metabolites, and organ clearance create feedback across tissues [87]. A renal decline may alter circulating metabolites and drug exposure, while pulmonary or cardiac deterioration changes oxygen delivery and venous congestion, which can further modify kidney and liver function [34,87]. Static scores summarize accumulated dysfunction but cannot fully identify the next transition or the mechanism driving it [7,87].

Dynamic prediction therefore requires repeated, event-aligned observations and models that distinguish patient state from treatment response [10,23,88,89]. State-space, joint longitudinal–event, landmark, or multi-state approaches can estimate transition probabilities, but their value depends on adequate time density, correct handling of informative missingness, and external calibration [7]. Two molecular time points may demonstrate short-term stability or change but rarely define a complex trajectory [10].

Diazepam-binding inhibitor/acyl-coenzyme A-binding protein (DBI/ACBP) illustrates a multi-level evidence chain. Circulating DBI/ACBP was associated with severity and mortality in human discovery and validation cohorts, while antibody neutralization improved bacterial clearance, survival, and organ function in three mouse sepsis models. The human component supports prognostic association, whereas therapeutic causality and safety remain animal-derived [70]. This distinction prevents a translational candidate from being represented as an adult treatment.

A clinically interpretable MODS model should estimate organ-specific deterioration over the next 24–48 h, identify influential time-varying factors, and link validated risk thresholds to potential clinical actions [7,25]. Risk estimates should update after major interventions or new data, accommodate irregular measurements and competing events, and distinguish prediction of deterioration from prediction of treatment benefit [14]. Prospective evaluation should separately assess first organ events, recurrent deterioration, recovery, and death, while reporting organ-specific and joint trajectories to determine whether models capture systemic transitions or dominant organ signals. Vital-sign trajectories can identify reproducible sepsis subphenotypes, whereas multi-omics studies suggest dynamic microbial, metabolic, and immune crosstalk but remain largely associative [60,90]. Clinical utility therefore requires sufficient actionable lead time, acceptable false-alert burden, and transportable trajectory estimates across ICUs.

5. AI-Guided Individualized Therapeutic Strategies

Precision therapeutic strategies currently span markedly different evidence levels, from available rapid diagnostics to model-based treatment-effect heterogeneity and preclinical target validation (Table 2) [4,12,14,70]. The table therefore separates diagnostic availability, observational treatment modeling, and experimental efficacy rather than placing them on a single scale [4,14,91]. Prognostic risk alone is insufficient for treatment selection because the highest-risk patient is not necessarily the patient with the greatest modifiable treatment effect.

Table 2. Precision therapeutic strategies in adult sepsis and their evidence maturity.

Therapeutic Domain	Precision Input/Endotype	Proposed Intervention/Decision	Current Evidence	Key Finding	Evidence Maturity	Next Step	Key Caution	Ref.
Antimicrobial therapy	Rapid pathogen identification, resistance markers, and host response	Earlier targeted therapy, escalation, or de-escalation	Diagnostic-platform and narrative clinical evidence	Rapid diagnostics may shorten time to actionable information when coupled with stewardship	Clinical diagnostic tools exist; precision-outcome evidence incomplete	Prospective trials of effective-therapy time antibiotic exposure and patient outcomes	Detection may represent colonization and may not provide susceptibility	[4]
Pathogen-specific stratification	Microbiome + metabolome profile	Pathogen- and resistance-aware antimicrobial selection	Exploratory pancreatitis-associated sepsis cohort of 11 patients	CRAB and carbapenem-resistant *E. coli* showed distinct microbial and metabolic profiles	Hypothesis-generating	Large pathogen-confirmed multicenter cohort with a locked classifier	Small selected cohort of 8 versus 3 patients with no external validation	[92]
Treatment-response stratification	Goal-directed multi-omics benefit scores	Select fluid or infection strategies by predicted treatment benefit	Prospective 43-hospital cohort of 1327 adults with serial clinical and multi-omics data and observational treatment-effect modeling	Goal-directed scores were more reproducible than single-omics clusters and identified heterogeneity in estimated benefit	Advanced observational evidence	Biomarker-stratified randomized trial with locked scores and prespecified interactions	Benefit was model-estimated rather than randomized and thresholds require prospective validation	[12]
Fluid therapy	Transcriptomic benefit score and six-protein surrogate	Restrictive versus usual fluid strategy	Multi-omics treatment-effect modeling in 494 adults	Predicted-strategy adherence was associated with lower mortality and the surrogate AUC was 0.802	Advanced observational evidence	Biomarker-stratified prospective randomized trial	Estimated benefit is not a randomized interaction	[14]
Hemodynamic optimization	Cardiac phenotype imaging perfusion and molecular markers	Dynamic vasopressor inotrope and fluid adjustment	Reviews and small exploratory multi-omics studies	Integrated imaging hemodynamics and biomarkers may define cardiomyopathy states	Conceptual/early clinical	Prospective multimodal time-series study with prespecified actions	No validated omics-guided policy and reinforcement-learning evidence remains insufficient	[84,85]
Immune-stimulatory therapy	Immunoparalysis/endotype and functional immune biomarkers	Select immunostimulatory treatment and timing	Precision-immunology reviews and biomarker-guided trial precedents	Multi-marker enrichment may better identify immune-low states	Conceptual to early clinical	Prospective companion-diagnostic trial with repeated immune monitoring	Immune states change over time; direct adult treatment-selection evidence remains limited	[9]
Immunometabolic therapy	Hyperinflammatory versus metabolic dysfunction phenotype	Phenotype-matched immune or metabolic modulation	Mechanistic and review evidence	PPAR mtDAMP IFN and oxidative-stress axes are candidate stratification mechanisms	Preclinical/ conceptual	Validated low-dimensional panel followed by an enriched intervention trial	Pathway activation does not establish net treatment benefit during active infection	[20,33]
Cardiomyopathy drug repurposing	Cardiac transcriptomic–metabolic network	Repurpose acetaminophen or pyridoxal phosphate	LPS-mouse multi-omics with network and experimental testing	Two prioritized compounds improved selected cardiac phenotypes in mice	Preclinical	Infectious models followed by dose safety biomarker and randomized studies	Network proximity and LPS efficacy do not demonstrate human benefit	[91]
DBI/ACBP-targeted therapy	High circulating DBI/ACBP and MODS phenotype	Neutralizing antibody to restore autophagy-supported host defense	Human observational cohorts plus three mouse models	Neutralization improved clearance survival and organ function in mice	Strong translational preclinical candidate	Human safety timing dose biomarker and randomized efficacy testing	Human treatment efficacy is untested; therapeutic causality is animal-derived	[70]

Abbreviations: ACBP, acyl-CoA-binding protein; AUC, area under the receiver operating characteristic curve; CRAB, carbapenem-resistant Acinetobacter baumannii; DBI, diazepam-binding inhibitor; IFN, interferon; LPS, lipopolysaccharide; MODS, multiple organ dysfunction syndrome; mtDAMP, mitochondrial damage-associated molecular pattern; PPAR, peroxisome proliferator-activated receptor.

5.1. Personalized Antimicrobial Therapy

Personalized antimicrobial therapy begins with reducing the time from empirical coverage to pathogen- and susceptibility-informed treatment while maintaining safety for rapidly deteriorating patients [3,4]. Multiplex PCR, T2 magnetic resonance, metagenomic sequencing, and rapid susceptibility platforms can accelerate microbiological information, but clinical value depends on coverage, specimen quality, distinction between colonization and infection, and availability of actionable resistance data. A faster positive result does not itself demonstrate earlier effective therapy or improved survival [4].

AI could combine organism detection, resistance markers, host-response signatures, prior antimicrobial exposure, infection source, and local epidemiology [48]. Host mitochondrial or transcriptomic patterns may differ across pathogen categories, but current evidence comes largely from public datasets and internally validated models [63]. Small pathogen-specific multi-omics cohorts are especially vulnerable to overfitting; an 11-person pancreatitis-associated sepsis study cannot support a locked antimicrobial-selection rule [92]. Proteomic and metabolomic signals associated with carbapenem-resistant organisms similarly remain exploratory without prospective testing in a realistic suspected-infection population [93].

The relevant endpoints extend beyond classification accuracy [7]. Studies should measure time to effective therapy, unnecessary broad-spectrum exposure, de-escalation, adverse drug events, source-control timing, resistance emergence, and patient-centered outcomes [3,4]. The counterfactual is also important: a negative molecular result should be shown to support safe narrowing or discontinuation rather than simply lower diagnostic probability [4]. A decision-support system should express uncertainty and defer to stewardship review when pathogen evidence and host-response evidence conflict [7,25]. Stewardship teams should be part of model design because the same result can require escalation, de-escalation, repeat sampling, or no change depending on source control and prior therapy [3,4].

Personalization also includes drug exposure after an antimicrobial has been selected. Machine-learning analysis of beta-lactam therapeutic drug monitoring has been used to identify adult sepsis subgroups in whom measured exposure may be associated with different outcomes [94]. Because monitoring and dose adjustment are confounded by illness severity, renal function, organism susceptibility, and clinician behavior, this approach requires prospective evaluation against protocolized pharmacokinetic targets rather than retrospective treatment–outcome association.

5.2. Dynamic Optimization of Fluid and Vasopressor Therapy

Uniform resuscitation can overlook differences in vascular tone, endothelial permeability, cardiac function, fluid responsiveness, venous congestion, and organ tolerance [78,84]. A prediction model estimates an outcome under observed care, whereas a dynamic treatment regime estimates how actions should change with evolving state, and reinforcement learning attempts to optimize a sequential policy. These outputs require stronger causal assumptions than ordinary risk prediction because treatment both responds to and changes the measured physiology [14] (Figure 2). At present, however, no omics-guided vasopressor policy has been prospectively validated in adult sepsis, and reinforcement-learning evidence remains insufficient to establish clinical treatment benefit.

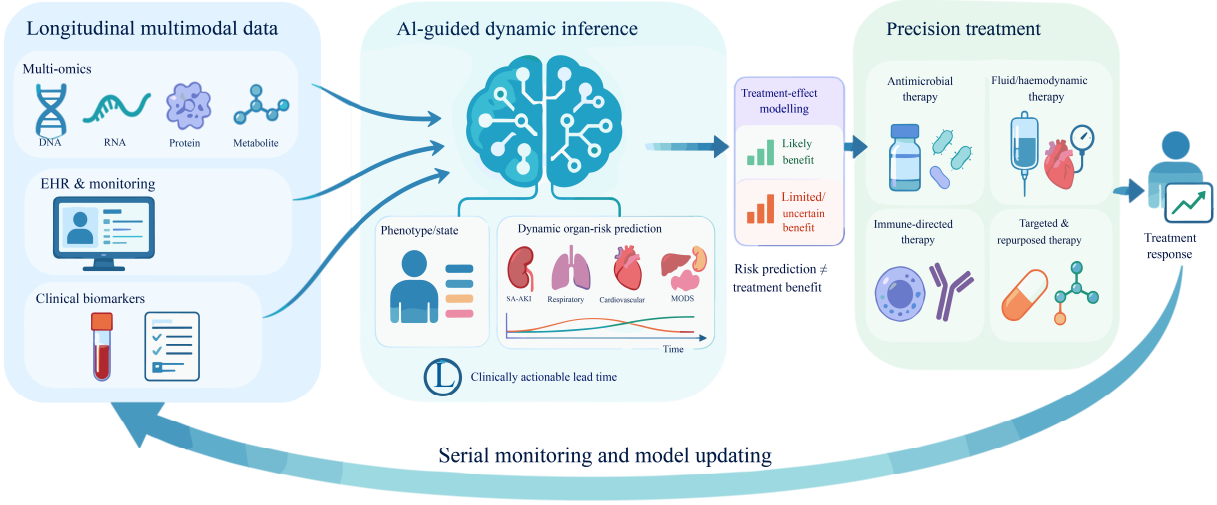


Figure 2. AI-enabled learning loop for precision sepsis care.

Longitudinal multimodal data integrating multi-omics profiles, EHRs, physiological monitoring, and clinical biomarkers provide complementary inputs for AI-guided dynamic inference. These data can support dynamic characterization of patient phenotypes or biological states and time-dependent prediction of organ-specific risks, including sepsis-associated acute kidney injury (SA-AKI), respiratory and cardiovascular dysfunction, and multiple organ dysfunction syndrome (MODS), with the aim of providing clinically actionable lead time. Importantly, risk prediction should be distinguished from prediction of treatment benefit. Treatment-effect modeling may identify patients with differential likelihood of benefit from antimicrobial, fluid or hemodynamic, immune-directed, targeted, or repurposed therapies. Treatment responses can subsequently be incorporated through serial monitoring and model updating, forming a continuous learning loop toward precision sepsis care. This pathway is a conceptual framework rather than an established clinical workflow and requires prospective clinical validation before implementation.

The most developed molecular example used 494 adults with septic shock to derive a transcriptomic score for model-estimated benefit from restrictive fluid therapy and a six-protein surrogate. Adherence to the model-predicted strategy was associated with lower mortality, and the protein surrogate reported an AUC of 0.802 for the transcriptomic benefit score. Treatment was not assigned by the biomarker, however, and the estimated mortality change was model-based rather than a randomized biomarker-by-treatment interaction [14]. The next evidentiary step is a prospective trial with a locked assay, predefined treatment rule, safety constraints, and interaction analysis [78].

Vasopressor and inotrope optimization requires integrated assessment of pressure, flow, perfusion, cardiac function, and treatment exposure [84,85]. However, current evidence does not support a validated omics-guided vasopressor policy or reinforcement-learning strategy for adult sepsis, and offline evaluation remains vulnerable to unmeasured confounding [25,95]. Biomarker-guided hemodynamic strategies should therefore undergo prospective evaluation and controlled impact testing before clinical implementation, with predefined safety constraints and model abstention for poorly represented patient states [78,84,85]. The goal is to complement, rather than replace, bedside physiology by identifying when similar physiological states may have different biological and treatment implications [14].

5.3. Immune Phenotype-Guided Therapy

Immune-guided treatment is motivated by the coexistence of hyperinflammation, endothelial injury, adaptive immune suppression, and mitochondrial or metabolic dysfunction [33,95]. These states can occur simultaneously and change within the same patient, making a single cytokine or one-time binary classification inadequate for treatment selection [9,95]. A useful companion profile should combine cell abundance, functional immune assays, protein mediators, transcriptional state, metabolic context, and repeated measurements [8,9].

Inflammatory endotyping has identified an interferon-γ–C-X-C motif chemokine ligand 9 (CXCL9)/C-X-C motif chemokine ligand 10 (CXCL10) axis, but the threshold, temporal stability, and ability to predict benefit from a specific immune intervention remain untested [11]. Immunoparalysis frameworks incorporate monocyte human leukocyte antigen-DR isotype (HLA-DR), lymphocyte dysfunction, and multi-omics states, yet definitions and clinical endpoints vary across studies [8,9]. Candidate T- or NK-cell markers such as granzyme M may track immune-effector state, but very small longitudinal single-cell cohorts and healthy-control receiver operating characteristic (ROC) do not establish a treatment rule [96].

The therapeutic direction must match both immune state and infection context [95,97]. Anti-inflammatory treatment may be harmful in a patient dominated by immune suppression, whereas immune stimulation could exacerbate uncontrolled inflammatory or endothelial injury [97]. Treatment enrichment therefore requires a prespecified biomarker-by-treatment interaction rather than a post hoc association between a biomarker and mortality [14]. Repeated target-engagement measurements should confirm that the intervention changes the intended immune state without compromising pathogen clearance [97].

Several mechanistic candidates illustrate the maturity gap. DBI/ACBP neutralization and Galectin-3 removal improved outcomes in animal models, but adult human evidence remains observational [70,98]. Peroxisome proliferator-activated receptor (PPAR), mitochondrial damage-associated molecular pattern (mtDAMP), inflammasome, neutrophil extracellular trap, and metabolic pathways provide plausible stratification axes, yet pathway activation alone does not establish net benefit during active infection [20,33,99]. These candidates belong in biomarker-enriched early-phase trials after assay validation, dose and safety studies, and confirmation of infection-related endpoints [97,100].

Pharmacodynamic readouts should be separated from predictive biomarkers [97]. A marker that falls after treatment may confirm target engagement without identifying who should receive the drug, while a prognostic marker may identify high risk without predicting treatment response [14]. Trials should therefore prespecify the enrichment

biomarker, target-engagement measure, infection-safety endpoint, organ endpoint, and interaction test [97,100]. Repeated measurements can then determine whether biological state conversion mediates clinical response or merely accompanies it.

Immune-treatment development is increasingly supported by integrated experimental systems. Neutrophil–endothelial interaction research combines organ-on-chip models, omics, immune phenotyping, and computational analysis to prioritize barrier-preserving strategies [101]. Single-cell and bulk transcriptomics can also identify treatment-associated immune shifts, as illustrated by observational ulinastatin studies [32]. Both approaches remain hypothesis-generating until treatment assignment is prospective and target engagement is linked to clinical benefit. Recent syntheses of personalized sepsis management reinforce that screening, prognosis, and therapy selection form distinct evidentiary steps [102]. Candidate immune or metabolic targets—including IL-1R2-related signaling, pyroptosis, and integrated dual-pathway strategies—should therefore enter biomarker-enriched trials only after analytical validation and infection-safety assessment [36,53,54].

5.4. AI-Driven Drug Discovery and Repurposing

In septic cardiomyopathy, network-based multi-omics analyses have prioritized drug-repurposing candidates that improved selected phenotypes in mice treated with lipopolysaccharide (LPS); however, network proximity and efficacy in LPS-induced models do not establish therapeutic benefit in adults with infection-associated cardiomyopathy [91]. Cross-layer prioritization of protein kinase cyclic adenosine monophosphate (cAMP)-activated catalytic subunit beta (PRKACB) received macrophage perturbation support, yet the experiment established participation in inflammatory output rather than therapeutic efficacy [13].

Translationally stronger target packages combine human association, mechanistic localization, perturbation, multiple infectious models, and a measurable companion biomarker. Even then, animal efficacy must be followed by pharmacokinetics, toxicology, dose selection, timing relative to infection control, and adult safety testing [70,98]. Renal-targeted nanoparticles carrying TAK-242 illustrate organ-specific delivery and experimental NF-κB/NLRP3 (NLR family pyrin domain containing 3) modulation, but biodistribution, ultrasound parameters, manufacturing, long-term safety, and effects on bacterial clearance remain unresolved [103].

Candidate development should proceed from computational nomination through orthogonal and functional validation, infection-relevant models, pharmacokinetic and safety assessment, adult biomarker selection, and randomized evaluation [7,13,21]. Prioritization should additionally consider clinically achievable exposure, organ distribution, effects of renal or hepatic dysfunction, infection clearance, and feasibility of biomarker-enriched trials [17,91,103]. Negative perturbation results should inform model refinement rather than be discarded, helping distinguish pathway association from target dependence [13]. AI can prioritize candidates but cannot replace these evidentiary steps. Ultimately, clinical development should link each candidate to a measurable biological state, explicit treatment window, and predefined monitoring of target engagement and infection-related harm.

6. Challenges and Future Perspectives

6.1. From Prediction to Clinical Intervention

Most sepsis multi-omics and AI studies remain retrospective, single-center, or dependent on public datasets, with limited prospective workflow evaluation [7,25]. External validation, prospective observational validation, clinical-impact evaluation, and biomarker-enriched treatment trials answer different questions and should be reported as separate evidence levels. A prediction becomes actionable only when the target population, time horizon, threshold, clinical response, comparator, and expected benefit–harm balance are specified [25,78].

The prospective towards Novel Biomarkers to Diagnose Sepsis protocol recruits patients across a broad emergency-care spectrum, but protocol publication alone does not provide evidence of predictive performance or clinical utility [104]. Silent deployment can evaluate data availability, turnaround, calibration, and alert burden before predictions influence care. A subsequent impact study must determine whether clinicians act on the output and whether those actions improve patient-centered outcomes without increasing unnecessary treatment [25]. Personalized treatment claims then require credible treatment-interaction evidence, ideally through biomarker-stratified randomization [14].

To move beyond retrospective performance claims, we propose a translational checklist spanning population definition, temporal anchoring, multimodal pairing, validation, clinical utility, treatment interaction, and deployment monitoring (Table 3). The checklist separates analytical validity, clinical validity, clinical utility, and implementation value because success at one level does not guarantee the next [7,25]. It also makes the intended inference explicit: diagnostic discrimination, future-event prediction, treatment-effect estimation, and implementation impact require different designs and cannot share one generic validation label.

Table 3. Translational quality checklist for multi-omics and artificial intelligence studies in adult sepsis.

Domain	Minimum Reporting	Why It Matters	Preferred Analysis/Evidence	Common Failure	Interpretation Rule	Ref
Population	Adult-only or separable adult results with explicit sepsis definition and setting	Age and setting materially affect host response and baseline risk	Report age inclusion criteria infection confirmation and source	Mixing age groups or using unclear syndrome labels	Do not extrapolate mixed-age findings without separable adult results	[1,2]
Comparator	Clinically confusable controls such as suspected infection or SIRS	Healthy-control separation exaggerates diagnostic performance	Include relevant differential diagnoses and subgroup performance	Reporting only sepsis-versus-healthy-control AUC	Healthy-control ROC supports discovery not clinical utility	[4,13]
Time anchor	Sampling relative to infection recognition, organ injury, and treatment	Sepsis biology and treatment exposure change rapidly	Use prespecified landmarks repeated sampling and event-aligned trajectories	Calling diagnosis-day sampling early prediction or two groups longitudinal	Prediction must precede the event and group time points do not prove individual trajectories	[10,18]
Multi-omics pairing	State whether modalities use the same patients and time points	Unpaired datasets cannot estimate within-person cross-omics relationships	Report pairing missingness batch processing and modality sample sizes	Calling parallel public datasets integrated multi-omics	Distinguish parallel evidence synthesis from paired multi-omics integration	[7,12]
Statistical unit	Use patients rather than cells or features as independent units	Cell-level pseudoreplication inflates precision	Use patient-level resampling mixed models and donor-aware validation	Splitting cells from the same patient across training and testing	Single-cell performance requires donor-level validation	[16,27]
Model development	Separate feature selection, tuning, and testing	Leakage and $p \gg n$ designs produce optimistic performance	Use nested resampling locked preprocessing optimism correction and full model specification	Selecting features before splitting or repeatedly testing overlapping subsets	Internal resampling is not external validation	[13,22]
External validation	Evaluate location-external and preferably time-external cohorts	Transportability is essential for multicenter ICU use	Report discrimination calibration subgroup performance and model updating	Reporting only training AUC or same-network validation	Performance without calibration and transport testing remains exploratory	[19,23]
Clinical utility	Define the action threshold comparator model and net benefit	A correct prediction may not improve care	Use decision-curve analysis workflow simulation prospective impact studies and patient-centered outcomes	Equating a high AUC with implementation readiness	Clinical utility requires incremental benefit over routine care	[7,25]
Treatment prediction	Test biomarker-by-treatment interaction rather than prognosis alone	High risk does not imply greater treatment benefit	Use causal treatment-effect modeling followed by biomarker-stratified randomization	Recommending treatment from mortality association or observational adherence	Personalized treatment claims require randomized or credible interaction evidence	[9,14]
Implementation and monitoring	Report turnaround cost missingness drift fairness and update policy	Performance changes across sites devices and populations	Use silent prospective evaluation version control drift monitoring and governance	Deploying static models without uncertainty or failure boundaries	Implementation evidence is separate from analytical and clinical validity	[7,105]

Abbreviations: AUC, area under the receiver operating characteristic curve; ICU, intensive care unit; ROC, receiver operating characteristic; SIRS, systemic inflammatory response syndrome.

6.2. Explainability and Clinical Trust

Explainability should clarify what the model learned, why a particular patient received a prediction, how uncertain the prediction is, and what action is justified [7,21,106]. A feature-attribution plot may reveal influential variables but does not demonstrate a biological mechanism or a causal treatment target [13]. Explanations should be tested for stability across resampling, sites, platforms, and plausible perturbations [7,22].

Proxy variables and leakage are especially important in critical care. A model may infer outcome from a treatment, test-ordering pattern, or measurement recorded after deterioration rather than from an early disease signal [25]. Molecular features can also encode cell composition, batch, nutrition, organ clearance, or prior therapy [18,37]. Explanation must therefore combine statistical attribution with temporal auditing, domain knowledge, and independent biological validation [7,21].

Clinical trust also requires explicit failure boundaries. The model should identify missing or out-of-distribution modalities, report uncertainty, and permit clinician override rather than returning a falsely precise recommendation [7]. Monitoring should include calibration drift, subgroup performance, false-alert burden, automation bias, and downstream actions [25].

6.3. Data Integration and Implementation

Multicenter implementation begins with shared definitions of adult sepsis, infection timing, treatment exposure, sampling windows, organ outcomes, and recovery trajectories [7,104]. Pre-analytical handling, assay platform, feature dictionary, model version, threshold, and update policy must be locked or explicitly harmonized [15,105]. Without these foundations, algorithmic sophistication cannot repair inconsistent labels or non-comparable molecular measurements [7,48].

Real-time deployment adds constraints that are absent from retrospective analysis [25,61]. Turnaround time, specimen availability, cost, laboratory staffing, missing modalities, device interoperability, and workflow burden determine whether a prediction arrives before the decision [61]. Models should be versioned with their assay, preprocessing pipeline, reference ranges, and threshold so that a laboratory or software update does not silently change the clinical tool [7,105]. Federated learning may support collaboration without centralizing all patient data, but it does not automatically correct site-specific labels, platform bias, unequal data quality, or fairness problems. Governance should define responsibility for monitoring, update approval, incident review, and withdrawal when performance deteriorates [7,25].

This review also has evidence-level limitations. The underlying literature is dominated by heterogeneous observational studies, public-data reanalyses, small single-cell cohorts, and preclinical mechanisms, while direct adult spatial multi-omics and biomarker-guided randomized trials remain scarce [7,17]. The selected core library prioritizes adult relevance and mechanistic depth but is not a formal meta-analysis, and rapidly changing AI methods and implementation standards may outpace a narrative synthesis [25]. We have therefore emphasized inference boundaries and reproducibility rather than pooling incomparable performance estimates.

6.4. Future Directions

In the near term, the field should prioritize adult multicenter cohorts with repeated blood and urine sampling aligned to infection recognition, treatment, organ injury, and recovery [7,19]. High-dimensional discovery should be translated into low-dimensional transcript, protein, metabolite, or immune-function panels with locked assays and external calibration [15,19]. These panels should be judged against routine clinical models for lead time, calibration, net benefit, and feasibility [7,25].

In the medium term, spatial and single-cell multi-omics should connect circulating states to kidney, lung, cardiac, and endothelial niches while preserving species and tissue boundaries [17,24]. Multimodal time-series models should integrate clinical data, continuous monitoring, imaging, and molecular panels, explicitly handling missing modalities and treatment–measurement feedback. Biomarker-enriched trials should test whether a molecular state modifies response to fluid, immune, antimicrobial, or organ-support strategies [9,14].

Longer-term priorities include foundation models, digital phenotyping, federated learning, and continuously updated systems, but these remain investigational in adult sepsis. Their translation requires transparent validation, drift monitoring, human oversight, and governance across analytical validity, clinical utility, treatment interaction, fairness, and safety [21,25].

Shared benchmark tasks should use temporally correct data splits, clinically realistic comparators, common outcome definitions, and reporting that exposes missingness and treatment leakage [7,25]. Patient and clinician involvement is also necessary to define acceptable alert burden, uncertainty displays, override pathways, and outcomes that matter beyond short-term mortality [25,61]. Sustained progress will depend less on a single

universal model than on interoperable evidence pipelines that can be audited, recalibrated, and prospectively re-evaluated as populations and care pathways change.

7. Conclusions

Multi-omics and artificial intelligence are advancing precision sepsis research by resolving biological heterogeneity and enabling dynamic risk stratification. However, most current signatures remain descriptive or prognostic rather than clinically actionable. Translation will require reproducible molecular assays integrated with longitudinal clinical data and validated across centers and care settings. Importantly, prediction of risk must remain distinct from prediction of treatment benefit, with therapeutic claims tested prospectively in biomarker-stratified randomized trials evaluating treatment-by-biomarker interactions. Ultimately, progress should be judged not by molecular complexity or peak model performance, but by whether these approaches enable earlier, interpretable, and transportable decisions that improve patient-centered outcomes.

Author Contributions

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT (OpenAI) to language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

List of Abbreviations

This list covers abbreviations used in the manuscript text, figure legend, and tables. Standard units of measurement, author initials, grant identifiers, and abbreviations appearing only in reference titles are excluded.

Abbreviation	Full Term
AI	artificial intelligence
AKD	acute kidney disease
AKI	acute kidney injury
ARDS	acute respiratory distress syndrome
AUC	area under the receiver operating characteristic curve
CBC	complete blood count
CD8	cluster of differentiation 8
CD35	cluster of differentiation 35; complement receptor type 1
CD35-uEV	CD35-positive urinary extracellular vesicle
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRP	C-reactive protein
CXCL9	C-X-C motif chemokine ligand 9
CXCL10	C-X-C motif chemokine ligand 10
cAMP	cyclic adenosine monophosphate
DBI/ACBP	diazepam-binding inhibitor/acyl-coenzyme A-binding protein
EARLI	Early Assessment of Renal and Lung Injury
EHR	electronic health record
EV	extracellular vesicle
HLA-DR	human leukocyte antigen-DR isotype
IC3	three-metabolite model comprising inosine, creatine, and 3-hydroxybutyrate
ICU	intensive care unit
IFN	interferon
IL-1R2	interleukin-1 receptor type 2
KDIGO	Kidney Disease: Improving Global Outcomes
LPS	lipopolysaccharide
MDW	monocyte distribution width
MEFISTO	Method for the Functional Integration of Spatial and Temporal Omics data
MODS	multiple organ dysfunction syndrome
mtDAMP	mitochondrial damage-associated molecular pattern
NAD+	oxidized nicotinamide adenine dinucleotide
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	natural killer
NLRP3	NLR family pyrin domain containing 3
PCR	polymerase chain reaction
PCT	procalcitonin
PPAR	peroxisome proliferator-activated receptor
PPARα	peroxisome proliferator-activated receptor alpha
PRKACB	protein kinase cAMP-activated catalytic subunit beta
qRT-PCR	quantitative reverse-transcription polymerase chain reaction
RNA	ribonucleic acid
ROC	receiver operating characteristic
ROSE	Reevaluation of Systemic Early Neuromuscular Blockade
S100A9	S100 calcium-binding protein A9
SA-AKI	sepsis-associated acute kidney injury
scRNA-seq	single-cell RNA sequencing
SIRS	systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SVM	support vector machine
SVM-RFE	support vector machine-recursive feature elimination
uEV	urinary extracellular vesicle

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