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REVIEW

Liu and Liang: Sepsis toxicity network reconstruction

Sepsis toxicity network reconstruction—Dynamic signaling and multi-organ injury: A review

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ABSTRACT

Sepsis is a complex systemic disease in which systemic toxicity—arising from inflammation–immune dysregulation, oxidative stress, programmed cell death (apoptosis, pyroptosis, ferroptosis), and metabolic reprogramming—drives multi-organ injury. The aim of this review was to synthesize how signaling pathways evolve within and between key organs (lungs, liver, kidneys, heart) and to evaluate whether multi-omics integration and network modeling can identify critical toxic nodes and predict disease progression. We conducted a narrative review of English-language mechanistic studies published between 2015 and 2025 in PubMed, Web of Science, and Scopus, supplemented by bibliography screening, while excluding case reports, conference abstracts, and non-mechanistic work. The evidence depicts a high-dimensional systemic network that remodels over time, with early pro-inflammatory modules transitioning toward immunosuppression and organ-specific injury patterns, while inter-organ propagation is mediated by damage-associated molecular patterns (DAMPs), exosomes, and metabolites. Oxidative stress and mitochondrial dysfunction, via reactive oxygen species (ROS), couple to pyroptosis and ferroptosis to reinforce toxicity loops, and computational approaches such as dynamic Bayesian networks (DBN) and graph neural networks (GNN) delineate regulatory hubs and support forecasting. Therapeutic progress has concentrated on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the NOD-, leucine-rich repeat and pyrin domain–containing protein 3 (NLRP3) inflammasome, and glutathione peroxidase 4 (GPX4), alongside artificial intelligence (AI)–assisted personalized toxicity maps and dynamic early-warning systems, though challenges remain in specificity, safety, and resistance. In conclusion, sepsis can be conceived as a temporally staged systemic toxicity network, and when combined with multi-omics, DBN/GNN modeling, and AI-enabled decision support, this framework offers a path toward individualized, mechanism-based care, while requiring rigorous validation to ensure clinical durability.

Keywords: Sepsis, systemic toxicity, network biology, multiple organ dysfunction, dynamic evolution of signaling pathways.

INTRODUCTION

Sepsis is a systemic condition triggered by infection, characterized by a dysregulated host response that leads to progressive organ dysfunction and, in many cases, death[1, 2]. It has long been recognized as one of the most formidable challenges in critical care medicine worldwide. According to data from a Global Burden of Disease study, approximately 49 million cases of sepsis occurred worldwide, resulting in around 11 million deaths—accounting for nearly 20% of all global deaths[3]. Despite advances in early recognition, prompt antimicrobial therapy, fluid resuscitation, and organ support over recent years, clinical outcomes for sepsis remain unsatisfactory, particularly in patients who develop multiple organ dysfunction syndrome (MODS) during the intermediate or late stages, with mortality rates reaching 40%–60%[4]. Traditionally, sepsis has been regarded as an immune hyperactivation syndrome driven by a cytokine storm[5, 6]. However, increasing evidence from both clinical and basic research indicates that immune activation and suppression do not act in isolation. Instead, they coexist and dynamically alternate, with complex interactions influencing the disease progression. For instance, some patients exhibit a pronounced pro-inflammatory response in the early stages, marked by elevated levels of IL-6 and TNF-α[7, 8], while others rapidly progress into an immunosuppressive state characterized by T cell exhaustion, impaired antigen presentation, and persistent infection[9, 10]. This clinical heterogeneity underscores that sepsis is not driven by a single pathological pathway, but rather by a complex systemic network involving immune dysregulation, metabolic reprogramming, cell death, oxidative stress, and microcirculatory disturbances[11, 12].

This evolving understanding has led researchers to move away from the traditional linear inflammation model and adopt perspectives centered on systemic toxicity and network regulation to redefine the pathophysiology of sepsis[13]. In this context, “dynamic evaluation” refers to the continuous and time-resolved assessment of signaling pathway evolution, immune status transitions, and organ-specific responses during the course of sepsis. This concept highlights that pathological changes are not

static but occur in a temporally staged manner, which provides opportunities to identify critical turning points for intervention. Within this framework, sepsis is conceptualized as a high-dimensional biological network composed of multiple signaling pathways that becomes destabilized and undergoes reconstruction under the influence of infection, metabolic dysregulation, and stress, ultimately leading to organ dysfunction and structural damage. In this review, "network reconstruction" is defined in a dual sense: (i) the biological remodeling of signaling and metabolic circuits during disease progression, and (ii) the computational and systems biology strategies (e.g., dynamic Bayesian networks, graph neural networks) that model and interpret these alterations. This expanded connotation emphasizes that the concept captures both the biological rewiring process in sepsis and the analytical methods used to study it. For instance, classical pro-inflammatory pathways such as NF-κB, MAPK, and JAK-STAT are rapidly activated during the early stages of sepsis to initiate host defense responses[12, 14]. However, insufficient negative feedback regulation can lead to sustained inflammatory injury. As the disease progresses, immunosuppressive pathways—including PD-1/PD-L1, IL-10, and SOCS (Suppressor of Cytokine Signaling) —are activated, suppressing immune cell function and resulting in a state of immune paralysis[15, 16]. Moreover, programmed cell death processes—including pyroptosis, ferroptosis, and necroptosis—along with mitochondrial dysfunction and energy metabolism disturbances, occur concurrently across multiple organs, collectively accelerating the systemic spread of toxicity[17-19].

However, the intertwined nature of multiple signaling pathways and biological processes makes it difficult for traditional single-factor approaches to fully elucidate the underlying mechanisms. Network biology and systems toxicology provide new frameworks for investigating sepsis. These fields construct interaction maps that highlight key pathways, central hubs, and coordinated changes in disease development [20, 21]. In sepsis research, particular attention is given to the dynamic remodeling of signaling pathways across various time points, organs, and immune states[12, 22]. This includes the migration and distribution of distinct immune cell types within the lungs, kidneys, and liver, contributing to both local and systemic

inflammation, as well as the critical role of NF-κB–NLRP3 inflammasome amplification in acute respiratory distress syndrome (ARDS) and sepsis-associated encephalopathy (SAE)[23, 24]. Meanwhile, the rapid advancement of multi-omics technologies—including single-cell transcriptomics, spatial omics, and time-series proteomic and metabolomic profiling—has enabled the dynamic tracking of key pathway alterations throughout the course of sepsis[25]. By integrating these data, more accurate dynamic regulatory models can be constructed using approaches such as dynamic Bayesian networks (DBNs), graph neural networks (GNNs), and multi-scale network fusion (MSF), enabling the identification of network control hubs and supporting the development of system-level intervention strategies.

Unlike many previous reviews that mainly adopt a static perspective or focus on isolated signaling pathways, the present review emphasizes the dynamic evaluation of systemic toxicity in sepsis. By highlighting how signaling pathways evolve across different time points, immune states, and organs, this review introduces an innovative framework that links network remodeling with multi-organ injury and cross-organ interactions. This narrative review focuses on the network reconstruction of systemic toxicity in sepsis, summarizing advances in dynamic signaling pathways, organ-specific injury, inter-organ coupling, and multi-omics modeling. By integrating these aspects, our work aims to provide readers with a novel systems-level perspective that may improve the understanding of disease heterogeneity and inspire precision-targeted strategies for sepsis management.

METHODS

This article is presented as a narrative review. We searched PubMed, Web of Science, and Scopus for English-language publications from 2015 to 2025 using combinations of the keywords “sepsis,” “systemic toxicity,” “multi-organ injury,” “network biology,” and “dynamic signaling pathways.” Additional references were identified by screening the bibliographies of relevant articles. Studies focusing on mechanistic insights into sepsis-associated systemic toxicity and multi-organ injury were included, while case reports, conference abstracts, and non-mechanistic studies were excluded.

No formal risk-of-bias assessment was conducted, as the purpose of this review was to provide a narrative synthesis rather than a systematic evidence appraisal.

Systemic toxicity mechanisms associated with sepsis

The inflammation–immune dysregulation network

One of the hallmark features of sepsis is an imbalanced immune response to infection, characterized by both excessive inflammatory activation and progressive immunosuppression. These processes may occur at different stages of the disease or simultaneously across various tissues, forming a complex inflammation–immune dysregulation network[26, 27]. In the early stages of disease, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate pattern recognition receptors such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), rapidly initiating signaling cascades including NF-κB, MAPK, and JAK-STAT, which trigger a burst release of inflammatory cytokines (e.g., IL-1β, TNF-α, IL-6), leading to a pro-inflammatory network-driven cytokine storm. Simultaneously, activation of the NLRP3 inflammasome amplifies both local and systemic inflammation by inducing pyroptosis and other forms of programmed cell death[28, 29]. At this stage, the signaling network exhibits high centrality, redundancy, and extensive pathway cross-talk, forming a tightly coupled inflammatory module characterized by multi-pathway synergy and positive feedback amplification. However, while pro-inflammatory mechanisms play a critical role in antimicrobial defense, their dysregulation may lead to extensive tissue damage and the propagation of systemic toxicity[30, 31].

During sepsis progression, the host initiates anti-inflammatory responses to counteract excessive immune activation[1]; however, this feedback mechanism is often overactivated, leading to immunoparalysis, with features such as T cell exhaustion, reduced HLA-DR expression on monocytes, impaired antigen presentation, and upregulation of immune checkpoint molecules such as PD-1 and CTLA-4[32, 33]. Sustained release of anti-inflammatory cytokines such as IL-10 and TGF-β, along

with increased levels of regulatory Tregs (T cells), marks a transition of the immune system from an activated to a dysfunctional state[34]. Studies have shown that this immunosuppression does not merely follow inflammation but occurs in parallel, establishing an "inflammation–immunosuppression coexistence" state[9, 26].

In sepsis, inflammation and immune dysregulation involve dynamic shifts in signaling networks. Initially, pro-inflammatory pathways such as NF-κB and MAPK dominate, but as the disease progresses, these pathways evolve into immunosuppressive modules like STAT3, IL-10, and PD-1, reflecting a temporal evolution in the immune response. This shift can be quantified through network parameters like centrality changes and reduced pathway efficiency. Spatial heterogeneity is seen across tissues: lung inflammation is driven by neutrophil infiltration and NLRP3, while antigen presentation and T cell apoptosis are impaired earlier in the liver, spleen, and lymph nodes. Thus, inflammation and immune dysregulation are part of a temporally evolving, spatially heterogeneous network driving systemic toxicity and organ dysfunction in sepsis[35].

Signaling pathways of apoptosis, necrosis, and regulated necrosis

Cell death represents a central event in the progression of systemic toxicity during sepsis, functioning not only as a consequence of tissue injury but also as a key driver of inflammation amplification, immune dysregulation, and multi-organ dysfunction[36, 37]. Early studies focused on classical apoptosis, in which Fas/FasL, TNF receptor signaling, and mitochondrial cytochrome c release activate caspase-3/9, leading to widespread apoptosis of immune cells (T cells, B cells, and dendritic cells), thereby impairing host immune responses and promoting immunoparalysis[38]. At the network level, this process is characterized by synchronized apoptosis among immune cell populations, downregulation of anti-apoptotic factors such as Bcl-2, and upregulation of pro-apoptotic receptors, collectively forming a stable and efficient immune exhaustion module. Meanwhile, hypoxia, energy metabolism disorders, and membrane disruption associated with sepsis can induce non-programmed necrosis,

resulting in the release of intracellular contents such as HMGB1 and ATP, which subsequently activate inflammasomes and TLRs, triggering an overflow-mediated toxic response[39, 40]. In recent years, the concept of regulated necrosis has significantly expanded our understanding of the cell death network, encompassing novel pathways such as pyroptosis, necroptosis, and ferroptosis, which serve as key links between inflammation and metabolic dysregulation (Table 1)[41]. Pyroptosis is characterized by NLRP3 inflammasome-mediated caspase-1 activation and GSDMD cleavage, predominantly occurring in neutrophils and macrophages, with marked involvement in ARDS and liver injury[42]. Necroptosis, driven by the RIPK1/RIPK3/MLKL axis, is typically triggered under caspase-8 inactivation and is closely associated with tissue necrosis across multiple organs[43]. Ferroptosis, driven by iron accumulation and lipid peroxidation, represents a key mechanism of injury in metabolically active cells such as cardiomyocytes and renal tubular epithelial cells[44]. These cell death pathways can be activated independently or synergistically, forming an interconnected network; for example, pyroptosis and necroptosis are often sequentially triggered within the same cell, amplifying inflammatory responses. More importantly, cell death pathways are not only regulated by inflammatory mediators but also reciprocally activate inflammatory signaling cascades such as NF-κB and STAT3, establishing a feedback loop of "cell death–inflammation amplification–systemic toxicity propagation."[45] From a dynamic network perspective, cell death signaling pathways in sepsis exhibit temporal staging and organ-specific spatial characteristics[46]. For instance, apoptosis predominates in immune cells during early phases, whereas pyroptosis and ferroptosis become more prevalent in parenchymal cells at later stages, indicating a progressive shift in dominant signaling nodes throughout disease evolution[47]. By integrating the aforementioned mechanisms, a network model of cell death-related pathways can be constructed to identify key cross-regulatory nodes (e.g., RIPK3, GSDMD, *GPX4*) as potential targets for systemic toxicity intervention, thereby providing a theoretical basis for multi-organ protection strategies.

Oxidative stress and mitochondrial dysfunction

Oxidative stress is a key pathological component of systemic toxicity in sepsis, spanning multiple phases including inflammatory activation, immune regulation, cell death, and multi-organ dysfunction[48]. It serves as a central and dynamically active module within the sepsis signaling network. Characterized by excessive accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) beyond the capacity of antioxidant systems (e.g., SOD, GSH, GPx), oxidative stress results in molecular damage and signaling dysregulation[49]. Mitochondrial dysfunction plays a central role by impairing ATP production, disturbing calcium homeostasis, and further amplifying ROS generation, thereby accelerating toxicity propagation across organs.

Rather than describing oxidative stress, inflammation, and cell death as separate events, it is more accurate to view them as an integrated pathogenic circuit. ROS activate NF-κB, MAPK, and NLRP3 inflammasome signaling, while simultaneously inducing ferroptosis through lipid peroxidation and GPX4 inhibition, creating a self-reinforcing loop of "oxidative stress–inflammatory amplification–cell death."

Organ-specific features are evident: pulmonary injury is characterized by NADPH oxidase–driven ROS bursts, while cardiac and renal tissues are particularly vulnerable to mitochondrial collapse.

Modern omics technologies and network modeling provide new opportunities to dissect this mechanism. Mitochondrial function can now be quantitatively tracked using single-cell metabolomics and spatial transcriptomics, while graph-based algorithms (e.g., PageRank, network path analysis) help identify regulatory bottlenecks in ROS signaling. Targeting antioxidant pathways such as Nrf2, GPX4, and SIRT3 has shown promise in mitigating oxidative stress–induced organ damage, though further validation is required.

Network-based dynamic evolution mechanisms of multi-organ injury

In addition to organ-specific injuries, recent studies highlight that systemic toxicity in sepsis is mediated by molecular carriers that propagate signals across distant organs. Damage-associated molecular patterns (DAMPs) such as HMGB1 and extracellular

ATP, exosome-derived microRNAs, and metabolic by-products (e.g., bile acids, lactate) serve as critical messengers in this process [39, 40, 44]. For example, exosomes released from inflamed pulmonary tissue can transfer miRNAs that upregulate TLR4 in renal tubular epithelial cells, thereby exacerbating acute kidney injury [18]. Similarly, hepatic HMGB1 and bile acid metabolites contribute to myocardial dysfunction and pulmonary inflammation, forming a liver–heart axis of injury [36, 37]. These inter-organ messengers enable local injury to trigger systemic amplification loops, transforming organ-specific damage into multi-organ dysfunction [31].

Pulmonary injury: Ards and disruption of the alveolar–capillary barrier

In sepsis, acute respiratory distress syndrome (ARDS) is among the earliest and most prevalent forms of organ dysfunction, primarily driven by the severe disruption of the alveolar–capillary barrier[24]. This barrier, composed of alveolar epithelial cells, capillary endothelial cells, and the basement membrane, is essential for maintaining pulmonary gas exchange. In ARDS, it is compromised by multifaceted immune and inflammatory responses, leading to increased permeability, alveolar edema, and hyaline membrane formation[52]. Neutrophil recruitment and hyperactivation play a key role in early lung injury by releasing elastase, myeloperoxidase (MPO), ROS, and forming neutrophil extracellular traps (NETs), which damage alveolar cells. Alveolar macrophages detect PAMPs and DAMPs through the TLR4–MyD88–NF-κB pathway, releasing pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α, further amplifying inflammation and recruiting more immune cells. Signaling pathways, including NF-κB, MAPK, JAK/STAT, PI3K-AKT, and the NLRP3 inflammasome, drive cytokine expression, pyroptosis, and pulmonary barrier disruption. The NF-κB–CXCL8–neutrophil axis and NLRP3–gasdermin D (GSDMD)–IL-1β pathway are central to the cytokine storm. Downregulation of tight junction proteins (e.g., ZO-1, VE-cadherin) and cytoskeletal remodeling via RhoA/ROCK and Src kinases contribute to barrier breakdown. Mitochondrial dysfunction and ROS accumulation

activate NLRP3, creating a feedback loop of oxidative stress, pyroptosis, cytokine release, and barrier disruption. ARDS progresses from a pro-inflammatory to a mixed pro- and anti-inflammatory network, shifting toward fibrosis. The lung, as a sentinel organ, affects distant organs like the kidney, liver, and heart, emphasizing the need for integrated multi-organ protection strategies. Unlike renal injury, pulmonary damage is dominated by barrier disruption via NF-κB–NLRP3–NETs axis, highlighting its unique role as the "first responder" in systemic toxicity.

Renal injury: Acute kidney injury (AKI)

In sepsis, acute kidney injury (AKI) is the most common organ dysfunction following ARDS, with an incidence exceeding 50%, and is strongly associated with increased mortality and progression to chronic kidney disease. Sepsis-associated AKI (SA-AKI) is now recognized not merely as a consequence of hypoperfusion, but as a manifestation of systemic toxicity driven by inflammation, metabolic dysregulation, and programmed cell death[53]. The pathogenesis is initiated by activation of pro-inflammatory pathways such as NF-κB and JAK/STAT via pattern recognition receptors including TLR4 and NOD1/2, leading to tubular epithelial release of IL-6, IL-1β, and MCP-1, which in turn promotes neutrophil and macrophage infiltration and local inflammatory amplification. Meanwhile, renal immune dysregulation—characterized by a predominance of M1 macrophages—and sustained activation of inflammatory cytokines contribute to a tightly coupled feedback network[20]. In SA-AKI, the mechanisms of cell death are complex, involving apoptosis (caspase-3/9 activation), pyroptosis (NLRP3–caspase-1–GSDMD axis), and ferroptosis (*GPX4* inhibition, lipid peroxidation). These pathways cause renal tubular damage and release DAMPs, which amplify inflammation, creating a toxic feedback loop of cell death, inflammation, and microenvironmental collapse. Oxidative stress and mitochondrial dysfunction also play key roles, with increased mitochondrial ROS production, suppressed Nrf2 antioxidant signaling, and dysregulated Keap1 activation driving ferroptosis and metabolic disturbances. Additionally, a shift from oxidative

phosphorylation to glycolysis in tubular cells disrupts ATP production and Na^+/Ca^{2+} transport. SA-AKI progresses from inflammation-driven signaling to metabolic imbalance and cell death, with shifts in central network nodes and reconfigured modules. Cross-organ inflammation, such as lung–kidney and liver–kidney axes, exacerbates renal injury, as shown by IL-6 and exosomal miRNAs upregulating TLR4 in renal tubules. Overall, SA-AKI represents a systemic network pathology, as illustrated in Figure 1. This renal pathology differs from pulmonary injury by emphasizing multi-mode cell death and metabolic imbalance as central drivers.

This figure illustrates the interconnected toxicity feedback loop among the kidney, lung, liver, and heart. Key pathways include NF-κB/JAK-STAT–IL-6/IL-1β signaling [53], the NLRP3–caspase-1–GSDMD pyroptosis axis [29], and ferroptosis mediated by *GPX4* inhibition [44].(Arrow colors: red = inflammatory amplification, blue = metabolic dysregulation, green = therapeutic modulation.) Drug annotations: BAY 11-7082 (NF-κB inhibitor, 5–20 μM) [11], MCC950 (NLRP3 inhibitor, 10 μM) [29], disulfiram (GSDMD inhibitor, 1–10 μM) [29], and *GPX4* agonists (ferroptosis protection) [44].

These pathways and agents represent potential intervention targets within the systemic toxicity network.

Hepatic injury and metabolic dysregulation

During the course of sepsis, the liver—as a central immunometabolic organ—is often affected early by systemic toxicity[36, 37, 54]. Hepatic dysfunction manifests not only as elevated transaminases and bilirubin abnormalities, but also as deeper network-level coupling among inflammatory, metabolic, and cell death pathways. In the inflammatory activation phase, Kupffer cells recognize PAMPs and DAMPs via receptors such as TLR4 and RAGE, activating NF-κB and JAK/STAT signaling, releasing TNF-α and IL-6, and initiating NLRP3 inflammasome-mediated pyroptosis, thereby damaging hepatocytes and sinusoidal endothelial cells, leading to microcirculatory dysfunction and regional hypoxia. Meanwhile, hepatocellular energy

metabolism undergoes reprogramming, with mitochondrial dysfunction, disruption of the TCA cycle, and impaired ATP production collectively contributing to metabolic stress. Suppression of nuclear receptors such as PPARα and FXR disrupts bile acid homeostasis, exacerbating cellular injury[55]. Accumulation of lipid peroxidation products (e.g., MDA, 4-HNE) activates ferroptosis pathways, establishing a synergistic toxic circuit involving inflammation, metabolic disturbance, and cell death.

Septic liver injury involves dynamic modular reconfiguration and signaling shifts. Initially, the NF-κB-driven pro-inflammatory module dominates, followed by NLRP3-pyroptosis and PPARα-metabolic modules in the middle stage, and later transitions to immunoregulatory pathways like IL-10 and TGF-β. Key nodes such as SIRT1, Nrf2, and *GPX4* regulate these transitions. The liver also acts as a source of inflammatory mediators, exosomes, and metabolic products that impact distant organs like the lung, heart, and kidney, creating a cross-organ signaling network. Septic liver injury is a systemic network process influenced by inflammation, metabolic disruption, and cell death, offering potential for multi-organ protection and precision therapy.

Myocardial injury and microcirculatory dysfunction

Septic cardiomyopathy (SCM) is a functional cardiac disorder driven by multiple factors, including inflammation, microcirculatory impairment, mitochondrial dysfunction, and calcium homeostasis disruption[56]. In the septic state, inflammatory cytokines such as TNF-α, IL-1β, and IL-6 activate NF-κB, JAK/STAT, and MAPK pathways on cardiomyocyte membrane receptors, inducing myocardial depressant factor release, calcium channel dysregulation, and programmed cell death. Concurrently, local immune cell infiltration and complement activation intensify myocardial inflammation, promoting apoptosis and contractile dysfunction. At the microvascular level, endothelial injury and imbalance of vasoactive substances (e.g., NO, endothelin) lead to heterogeneous myocardial perfusion, further contributing to

metabolic derangement and oxidative stress. Mitochondrial dysfunction in cardiomyocytes is characterized by loss of membrane potential, mitochondrial permeability transition pore (mPTP) opening, and excessive ROS release, which collectively inhibit ATP production and activate the caspase cascade, leading to cell death[57]. Concurrently, calcium dysregulation exacerbates injury, with Ca^{2+} overload impairing myofilament contraction and activating calpain-mediated cytoskeletal degradation. At the network level, the signaling evolution of SCM demonstrates dynamic remodeling, transitioning from inflammation-dominated pathways to those centered on metabolism and cell death. Early dominant signals such as NF-κB and STAT3 are progressively replaced by ROS, mPTP, and Nrf2-related pathways, with late-stage activation of reparative modules including TGF-β and VEGF. Multiple pathways converge on shared regulatory nodes (e.g., NF-κB, iNOS, *GPX4*), forming a high-density toxic module with dynamically shifting signal intensity and centrality during disease progression. Moreover, cardiac dysfunction exacerbates damage to other organs through hypoperfusion and circulatory instability, contributing to complications such as AKI and intestinal barrier breakdown. Simultaneously, pulmonary inflammatory mediators can disseminate via the bloodstream to the myocardium, triggering localized inflammatory responses and forming a typical inter-organ toxic loop. Collectively, SCM represents a multi-pathway systemic toxicity network shaped by inflammation, microcirculatory disruption, and metabolic collapse. A deeper understanding of its evolutionary trajectory and network remodeling mechanisms may offer novel targets for multi-organ protection.

Methods and tools for reconstructing systemic toxicity networks

Integrated analysis strategies for multi-omics data

The systemic toxicity of sepsis involves the coordinated evolution of multiple biological systems and pathways—including inflammation, immunity, metabolism, and regulated cell death—characterized by high complexity, temporal dynamics, and inter-individual heterogeneity. Traditional single-omics approaches are insufficient to

capture this complexity, whereas multi-omics integration has emerged as a key strategy for uncovering the underlying mechanisms of network remodeling[58, 59]. Common omics layers, including transcriptomics, proteomics, metabolomics, epigenomics, and single-cell/spatial omics, capture distinct biological aspects such as gene expression, protein translation, metabolism, and cellular heterogeneity. Integration strategies fall into three categories: early integration merges data for joint dimensionality reduction; intermediate integration models each omic independently before aligning biologically using pathways or co-expression networks; late integration analyzes heterogeneous datasets after individual modeling. Analytical tools like iCluster, MOFA, and SNF reduce multi-omics features, while Cytoscape and OmicsNet enable network visualization. GNNs and Bayesian modeling are useful for dynamic process inference[60]. In sepsis, multi-omics studies reveal NF-κB and NLRP3 signaling drift across organs, highlighting inflammation network heterogeneity. Combined metabolomic and proteomic analyses show *GPX4*-mediated ferroptosis in both renal and myocardial tissues. Multi-omics integration aids in constructing regulatory networks and identifying key signaling pathways, but faces challenges such as data heterogeneity and computational complexity. Emerging approaches such as causal inference and spatial transcriptomics may further enhance biological resolution[61]. In other diseases, multi-omics and dynamic evaluation have also been widely applied. For example, in oncology, longitudinal single-cell and spatial transcriptomics have been used to map tumor evolution and therapeutic resistance[62]; in neurodegenerative disorders such as Alzheimer's disease, time-series metabolomics and proteomics have revealed progressive mitochondrial dysfunction and synaptic loss[63]; and in cardiovascular research, integrative omics combined with network modeling has identified dynamic lipid metabolism and immune-inflammatory interactions driving atherosclerosis progression[64]. Compared with these studies, our review highlights a unique perspective in sepsis by emphasizing multi-organ, cross-system coupling and network reconstruction of systemic toxicity, rather than static or organ-restricted models. Computational modeling frameworks for multi-omics integration are detailed in Section 5.2. Overall,

multi-omics offers valuable insights into the dynamic signaling evolution and network remodeling in sepsis toxicity (Figure 2).

This figure illustrates computational methods used to integrate heterogeneous omics data for network reconstruction. Approaches include weighted gene co-expression network analysis (WGCNA) [65], dynamic Bayesian networks (DBNs) [25], and graph neural networks (GNNs) [58]. (Arrow colors: black = data integration flow, orange = iterative refinement using AI models.)

Node colors: yellow = key signaling pathways (e.g., NF-κB, NLRP3, *GPX4*), blue = metabolic regulators, purple = immune checkpoints.

AI-driven models: indicate the application of machine learning and deep learning (e.g., GNNs, recurrent neural networks) to capture dynamic and cross-organ regulatory relationships.

Network modeling and dynamic simulation methods

Building upon the multi-omics integration strategies outlined in Section 5.1, network modeling provides the analytical framework to reconstruct dynamic interactions underlying sepsis. Early static models, such as protein–protein interaction (PPI) networks, co-expression networks (e.g., WGCNA), and transcription factor–miRNA–target gene networks, have advanced understanding of structural interactions in sepsis[65]. However, they fail to capture dynamic changes during disease progression. To overcome these limitations, advanced modeling approaches—including dynamic Bayesian networks (DBNs), ordinary differential equation (ODE) frameworks, Boolean networks, and graph neural networks (GNNs)—have been developed to infer temporal signaling dynamics and cross-organ interactions. To model multi-organ injury, strategies such as multilayer networks, cell–cell communication tools (e.g., CellChat), and tissue-specific networks have been developed, enabling the study of signal coupling and toxicity across organs. Notable findings include the identification of the STAT3–iNOS module in myocardial toxicity networks. Despite challenges like data heterogeneity and temporal resolution, the

integration of omics, spatiotemporal data, and AI-driven models promises to improve predictive and intervention strategies in sepsis (Table 2).

A direct comparison of these modeling strategies highlights their distinct applicability in capturing the temporal–spatial complexity of sepsis. DBNs are particularly advantageous for inferring causal activation orders of signaling pathways under incomplete data, but their high computational cost and requirement for finely resolved time-series data limit large-scale applications [66]. ODE-based frameworks offer strong mechanistic interpretability and high-resolution simulation of biochemical kinetics, yet they demand extensive prior knowledge of parameters and are highly sensitive to data quality. Boolean networks, while computationally efficient and suitable for exploratory analyses in low-data contexts, provide only binary state transitions, making them less capable of modeling graded or continuous molecular dynamics [67]. In contrast, GNNs excel at integrating heterogeneous multi-omics and multi-organ data, enabling the reconstruction of high-dimensional toxicity networks with nonlinear interactions; however, they require large datasets, complex training, and may suffer from reduced interpretability compared with mechanistic models [68]. Collectively, these features suggest that no single method is universally optimal, and hybrid or multi-model strategies may be most effective for sepsis toxicity network modeling.

Therapeutic target identification and prospects for precision intervention

Research progress in systemic toxicity intervention strategies

Sepsis-induced systemic toxicity results from the dysregulation of multiple signaling pathways, cell death, metabolic imbalance, and immune dysfunction. Consequently, therapeutic strategies are shifting from traditional anti-inflammatory and organ support approaches to systemic regulation targeting key network nodes. At the signaling level, NF-κB, JAK/STAT, and the NLRP3 inflammasome are critical targets[69]. Small-molecule inhibitors like BAY 11-7082, ruxolitinib, and VX-765 block pro-inflammatory pathways, reducing multi-organ injury risk. Advances in

targeting programmed cell death, especially pyroptosis and ferroptosis, have led to agents such as MCC950, disulfiram, and *GPX4* agonists that interrupt the inflammation–cell death loop[70]. Metabolic reprogramming via Nrf2 activation or AMPK agonists improves antioxidant capacity, mitochondrial function, and energy metabolism, alleviating organ dysfunction[71]. Immune reconstitution strategies like IL-7 supplementation and PD-1/PD-L1 blockade restore T cell function and antigen presentation[72]. In summary, these therapeutic advances highlight the importance of pathway-specific and multi-target interventions for systemic detoxification and organ protection.

Personalized medicine and dynamic early warning systems

Beyond pathway-targeted therapies, personalized medicine is essential to address the heterogeneity of sepsis patients. By integrating multi-omics data—including transcriptomics, proteomics, metabolomics, single-cell RNA sequencing, and spatial transcriptomics—a "systemic toxicity atlas" can be created for each patient[73]. This atlas enables the mapping of key signaling pathways such as NF-κB, NLRP3, JAK/STAT, and *GPX4* across organs, identifying individualized toxicity network hubs. Unlike traditional static systems like SOFA, time-series models—such as DBNs, GNNs, and recurrent neural networks (RNNs)—offer greater precision in predicting complications like ARDS, AKI, and MODS[74]. AI platforms can integrate electronic medical records, real-time monitoring data, and omics profiles to guide interventions dynamically[75]. The development of digital twins enables in silico patient-specific models that simulate therapeutic outcomes and enable closed-loop treatment adjustments[76, 77]. Collectively, these strategies shift sepsis care toward precision-driven, mechanism-based management, complementing the therapeutic advances summarized in Section 6.1.

Limitations

This narrative review has several limitations that should be acknowledged. First, as a non-systematic review, there is an inherent risk of selection bias in the studies cited,

despite our efforts to cover the most relevant literature. Second, the synthesis relies largely on secondary data from published reports, which may themselves be subject to methodological heterogeneity and varying quality. Third, the primary studies included in this review exhibit substantial heterogeneity in experimental models, patient populations, and analytical approaches, limiting the direct comparability of findings. Finally, the discussion on AI-driven "toxicity atlases" and predictive modeling remains speculative at this stage, requiring further empirical validation before clinical translation. These limitations highlight the need for cautious interpretation of our conclusions and emphasize that the concepts presented here should be regarded as hypothesis-generating rather than definitive.

Beyond these methodological considerations, important translational challenges also deserve attention. Organ-specific drug delivery hurdles continue to restrict the efficacy of pathway modulators, while potential off-target effects and adaptive resistance mechanisms may compromise long-term outcomes. At the clinical level, variability among patient populations, regulatory requirements, and the lack of standardized implementation protocols represent additional barriers that complicate bedside application. Moreover, AI-driven warning systems, though conceptually promising, require high-quality, large-scale, and interoperable datasets; issues of interpretability, real-time data integration, and rigorous clinical validation remain unresolved. Together, these translational barriers underscore that while systemic toxicity network-based interventions hold great potential, substantial work is still needed before they can be safely and effectively applied in sepsis care.

CONCLUSION

Sepsis, as a systemic disease, is not driven solely by inflammation or perfusion deficits but rather by a system-wide toxicity network reconstruction process involving inflammation, immune dysregulation, metabolic disturbances, programmed cell death, and multi-organ dysfunction. With advancements in multi-omics technologies, network biology, and dynamic modeling, researchers have progressively elucidated the spatiotemporal evolution of key signaling pathways—including NF-κB,

JAK/STAT, NLRP3, and *GPX4*—across different organs, resulting in the construction of a comprehensive toxicity map characterized by multi-pathway, multi-node, and multi-organ coupling. This review takes systemic toxicity as a central framework to comprehensively summarize the mechanisms of signaling pathway remodeling, organ injury evolution, and network modeling strategies. It further outlines recent advances in therapeutic interventions including pathway modulation, regulation of cell death, metabolic reprogramming, and immune remodeling. In addition, we highlight the potential of multi-omics–driven personalized toxicity mapping, AI-assisted risk prediction models, and closed-loop feedback control systems in achieving individualized precision medicine. Future research should focus on multidimensional data integration, causal graph modeling, cross-organ network prediction, and digital twin technologies to advance systemic toxicity from mechanistic understanding to controllable modulation. In conclusion, this narrative review provides a systemic toxicity–centered perspective that offers a more comprehensive understanding of the pathophysiology of sepsis, laying a solid foundation for multi-organ protection and precision therapy. However, further research is needed to address the challenges of integrating multi-omics data and refining intervention strategies. Marking a critical transition in critical care medicine toward systematization, personalization, and intelligent management.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Comparative table of sepsis-associated cell death mechanisms

Type of cell death	Activation mechanism	Key pathways molecular signals	Functional implications
Apoptosis [38](Programmed Cell Death)	Fas/FasL activation, cytochrome c release, caspase-3/9 activation	Bcl-2↓, caspase-3/9↑	Immune cell loss and immunoparalysis
Necrosis [39, 40](Unregulated Cell Death)	Hypoxia, energy depletion, membrane rupture	HMGB1↑, extracellular ATP↑ → TLR/NLRP3	Release of DAMPs, inflammation amplification
Pyroptosis[28, 29, 42]	NLRP3 inflammasome → caspase-1 → GSDMD cleavage	NLRP3↑, caspase-1↑, IL-1β↑	Inflammatory amplification, ARDS/liver injury
Ferroptosis[44]	Iron overload, lipid peroxidation	Fe^{2+}↑、*GPX4*↓、MDA↑、4-HNE↑	Lipid peroxidation–mediated injury in heart/kidney
Necroptosis[43]	RIPK1/3 → MLKL	RIPK1↑, RIPK3↑, MLKL↑	Amplifies necrosis and immune activation

Note: ↑ indicates upregulation/increase; ↓ indicates downregulation/decrease. Abbreviations: Bcl-2, B-cell lymphoma 2; HMGB1, high mobility group box 1; ATP, adenosine triphosphate; TLR, toll-like receptor; NLRP3, NOD-like receptor family pyrin domain-containing 3; GSDMD, gasdermin D; IL-1β, interleukin-1 beta; ARDS, acute respiratory distress syndrome; Fe^{2+}, ferrous iron; GPX4, glutathione peroxidase 4; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; RIPK1, receptor-interacting serine/threonine-protein kinase 1; RIPK3, receptor-interacting serine/threonine-protein kinase 3; MLKL, mixed lineage kinase domain-like protein; DAMPs, damage-associated molecular patterns.

Table 2. Comparative analysis of modeling approaches

Model types	Representative methods	Modeling features	Applicable scenarios	Advantages	Challenges
Static Networks[58, 65]	PPI, WGCNA, TF–miRNA	Interaction-based network construction; regulatory relationship inference	Pathway co-expression; transcriptional regulation inference	Clear structure, suitable for early screening	Inability to simulate time variation; weak dynamic prediction
Dynamic Bayesian Networks[46]	DBN	Node states vary over time; sequence-based modeling	Pathway activation order, signal propagation dynamics	Capable of handling incomplete data; supports temporal inference	High computational complexity; time-dependent data labeling required
ODE-based Systems[46]	ODE frameworks	Continuous modeling of dynamic transitions	Biochemical kinetics, pathway activity prediction	High quantitative resolution; mechanistic interpretability	Requires large prior parameter sets; sensitive to data quality
Boolean Networks[46]	Boolean Network	Binary-state modeling of on/off	Logical state transition analysis	Simple structure, suitable for	Difficult to model continuous

		mechanisms		low-data or multi-state systems	transitions; lacks quantitative expressiveness
Graph Neural Networks [25, 58]	GCN, GAT, Hetero-GNN	High-dimensional graph learning; inter-organ/multi-omic integration	Multi-organ signaling network integration	Strong nonlinear modeling capacity; adaptable to complex systems	Requires large datasets; interpretability may be limited
Multilayer/Cross-organ Networks[25, 58]	CellChat, tissue-GNN	Integrates cell–cell, tissue–organ, and spatial layers	Signal cross-talk, spatially resolved organ interaction networks	Captures cross-scale and spatial interactions; supports spatial modeling	High data demands; model complexity and parameter tuning required

Abbreviations: PPI, protein–protein interaction; WGCNA, weighted gene co-expression network analysis; TF, transcription factor; miRNA, microRNA; DBN, dynamic Bayesian network; ODE, ordinary differential equation; GCN, graph convolutional network; GAT, graph attention network; GNN, graph neural network.

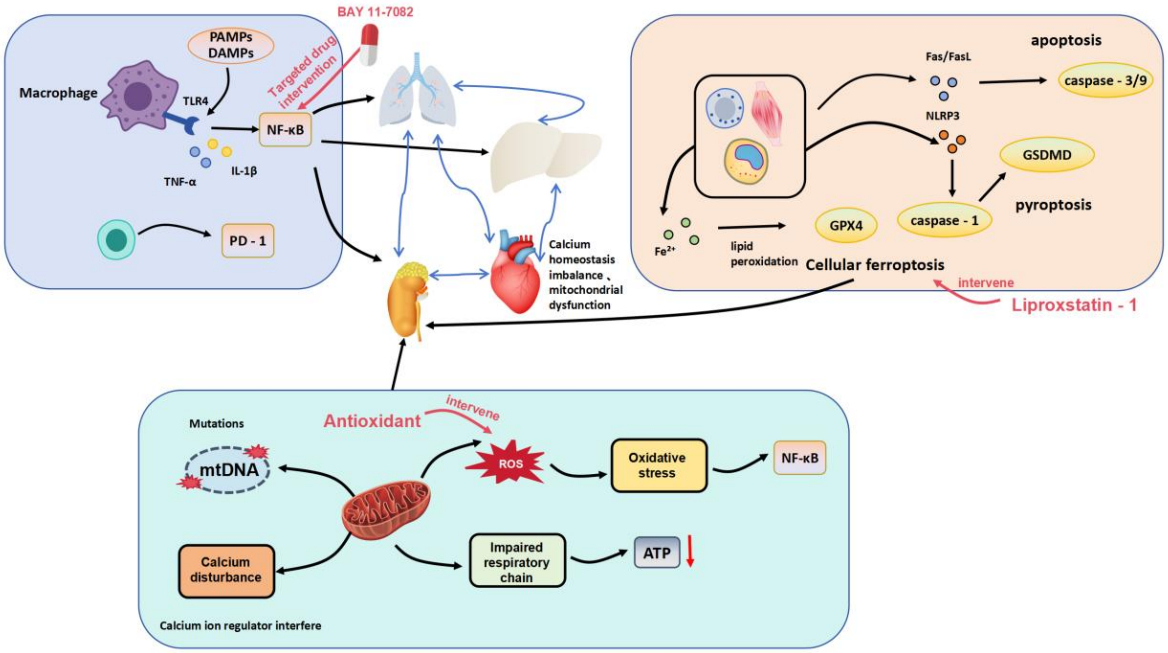

Figure 1. Schematic representation of the systemic toxicity network in sepsis-associated acute kidney injury (SA-AKI). The figure shows the interconnected feedback loops among kidney, lung, liver, and heart. Pathways illustrated include inflammatory signaling (NF-κB, cytokines), mitochondrial dysfunction (mtDNA mutations, ROS, ATP depletion), and programmed cell death mechanisms (apoptosis, pyroptosis, ferroptosis). Therapeutic interventions (BAY 11-7082, Liproxstatin-1) are indicated. Arrow colors: red = inflammatory amplification, blue = metabolic dysregulation, green = therapeutic modulation. Abbreviations: PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; IL, interleukin; PD-1, programmed cell death protein 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; ATP, adenosine triphosphate; GPX4, glutathione peroxidase 4; Fas/FasL, Fas receptor/Fas ligand; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; GSDMD, gasdermin D.

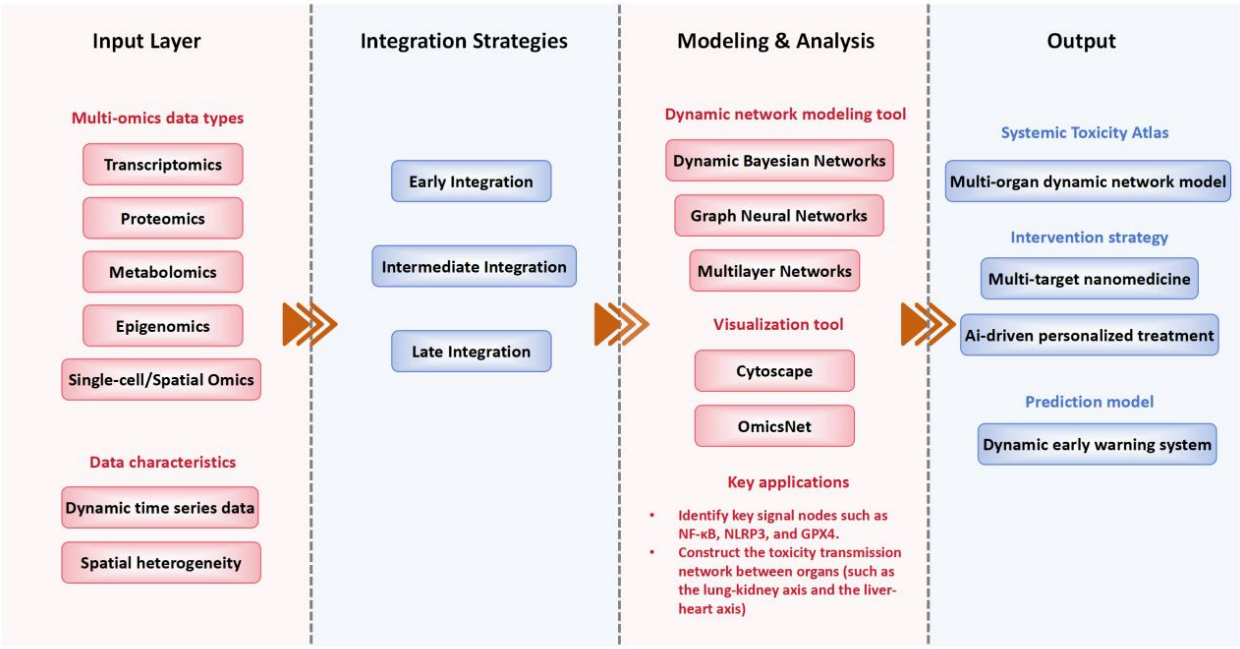

Figure 2. Computational frameworks for multi-omics integration and dynamic network reconstruction in systemic toxicity of sepsis. The figure shows input omics layers, integration strategies, modeling and visualization tools, as well as key applications and resulting outputs. Abbreviations: DBN, Dynamic Bayesian Network; GNN, Graph Neural Network; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; GPX4, Glutathione Peroxidase 4.