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Review Article

Precision Management of Sepsis-Induced Atrial Fibrillation: Current Landscape and Future Directions of Integrated Multi-Omics and Artificial Intelligence Research

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Abstract

Research on the application of multi-omics and artificial intelligence (AI) in sepsis-associated atrial fibrillation (SA-AF) has progressed, yet significant translational bottlenecks remain. Firstly, the depth of multi-omics integration is inadequate. Most analyses are still confined to single-omics approaches, lacking systematic cross-omics integration and dynamic temporal data, which hampers the elucidation of molecular mechanisms and causal relationships. Molecular discrepancies between peripheral blood and atrial tissue further limit the accuracy of biomarkers. Secondly, AI models commonly suffer from weak generalizability, overfitting due to small sample sizes and data bias, and often lack external validation and mechanistic interpretability. Being predominantly static, these models struggle to adapt to the dynamic progression of sepsis. Thirdly, target translation and drug development face challenges, including insufficient target specificity potentially leading to off-target risks, species differences and patient heterogeneity hindering preclinical translation, and unverified safety of precision delivery systems. Future research needs to establish a multi-level, dynamically integrated multi-omics and AI analytical framework, incorporating longitudinal data and causal inference methods (e.g., Mendelian randomization) to validate targets. Furthermore, employing tissue-specific inference and single-cell technologies to decipher the immuno-electrophysiological interaction network is crucial to advance the precision prevention and management of SA-AF.

INTRODUCTION

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, is a leading cause of mortality in intensive care units globally. Among its complications, new-onset atrial fibrillation (NOAF) has increasingly become a major clinical concern [1,2], significantly associated with elevated mortality, prolonged hospitalization, and increased healthcare costs. Despite epidemiological evidence highlighting this association, the precise molecular mechanisms linking sepsis to atrial fibrillation (AF) remain incompletely elucidated, resulting in a lack of targeted therapeutic strategies. This clinical challenge reflects the multidimensional pathophysiological interplay between these two complex conditions. Conventional understanding suggests that factors such as systemic inflammation, autonomic dysfunction, electrolyte imbalances, and myocardial injury collectively contribute to AF development in sepsis [3]. However, such broad pathophysiological insights have not translated effectively into precise clinical interventions. With the growing emphasis on precision medicine, the need for individualized risk prediction and targeted therapies in managing sepsis-associated AF has become increasingly urgent.

Recent advances in multi-omics technologies—encompassing genomics, transcriptomics, proteomics, and metabolomics [4,5]-coupled with the rapid development of artificial intelligence (AI) algorithms [6], offer novel

avenues to address this challenge. These approaches enable the extraction of complex, non-obvious patterns from vast biological datasets, uncovering underlying disease mechanisms and providing unprecedented opportunities to decipher the intricate network linking sepsis and AF, identify high-risk patients, and discover novel therapeutic targets. This review aims to systematically outline the current applications of multi-omics and AI in sepsis-associated AF research, analyze existing limitations, and propose future directions to advance the field toward a precision medicine framework.

Elucidating Molecular Mechanisms Through Multi-Omics Technologies

The widespread adoption of high-throughput detection technologies has expanded omics research from single-genome analyses to multiple layers, including transcriptomics, proteomics, and metabolomics, providing rich data support for comprehensively dissecting the molecular mechanisms of sepsis-associated atrial fibrillation (AF) (Table 1). Transcriptomic studies have been the most active in this field. Analyses of AF patients have identified numerous differentially expressed genes significantly enriched in biological processes such as immune response, calcium signaling pathways, and muscle system processes [7-9]. Notably, research on sepsis-induced myocardial injury has revealed that m6A RNA methylation [10], mediated by the methyltransferase METTL3, coordinates inflammation, apoptosis, and ferroptosis through transcriptomic reprogramming. This finding offers a new perspective for understanding how sepsis influences cardiac electrophysiology via epigenetic regulation. Furthermore, the dual role of exosomes in intercellular communication is being gradually uncovered—they can propagate pyroptosis through the microRNA-885-5p/HMBOX1 axis [11], while also delivering therapeutic substances such as microRNA-223 to suppress inflammatory responses [12].

In proteomics, an innovative study focused on the role of protein lactylation in sepsis-induced myocardial injury. By integrating multi-omics technologies with artificial intelligence algorithms, the study found that lactylation at lysine residues K166 and K728 of the trifunctional enzyme subunit alpha (HADHA) inhibits its activity, leading to mitochondrial dysfunction, reduced ATP production, and ultimately impaired myocardial contractility [13]. This discovery not only establishes a direct link between metabolic alterations and myocardial function but also suggests a potential therapeutic target for intervention.

Progress has also been made in epigenomics and metabolomics. Research indicates that sepsis-induced alterations in histone modifications [14], DNA methylation [15], and non-coding RNA expression [16], may simultaneously affect immune cell activity and cardiomyocyte electrophysiological properties, forming an "immuno-electrophysiological" cross-regulatory network. The elucidation of these upstream regulatory mechanisms provides a theoretical foundation for developing combined therapeutic strategies that target both inflammation and arrhythmia.

ADVANCEMENTS IN ARTIFICIAL INTELLIGENCE-BASED PREDICTIVE MODELS

In the field of risk prediction for sepsis-associated atrial fibrillation (AF), machine learning algorithms are demonstrating significant potential. Multiple studies have attempted to develop predictive models by integrating clinical data with molecular features, aiming to achieve early identification of high-risk patients [17]. One transcriptomic study on AF developed a machine learning-based diagnostic model. It further validated gene expression using qRT-PCR in an AF mouse model, where six key genes related to lactate metabolism exhibited transcriptomic changes correlated with the AF phenotype and CD4+/CD8+ T cell populations. A diagnostic model utilizing these genes achieved an AUC of 0.909 in an external validation dataset [18]. This finding suggests that machine learning models based on molecular features offer considerable advantages in identifying AF risk.

A similar research approach has been applied to predict sepsis-related organ injuries. A study on sepsis-induced

Table 1: Application of Multi-Omics Technologies in Sepsis-Associated Atrial Fibrillation Research

Omics type	Key technologies	Main findings	Clinical significance
Transcriptomics	Single-cell sequencing, RNA-seq	Abnormal immune response, calcium signaling pathway disorder, and m6A methylation modification	Reveal cell-specific expression patterns and identify immune-electrophysiological cross-dialogues
Proteomics	Mass spectrometry analysis, lactation modification group	The lactation of HADHA leads to energy metabolism disorders and mitochondrial dysfunction	Provide new therapeutic targets and connect metabolic alterations with electrophysiological disorders
Epigenetic group	ChIP-seq, ATAC-seq	Mettl3-mediated m6A modification and histone modification	Explain the regulatory mechanism of environmental factors on gene expression
Metabolomics	LC-MS, GC-MS	Fatty acid oxidation damage and lactic acid accumulation	Discover early diagnostic biomarkers to reveal metabolic reprogramming

acute respiratory distress syndrome (ARDS) and sepsis-induced cardiomyopathy (SIC) successfully identified five key genes—including LCN2, AIF1L, STAT3, SOCS3, and SDHD—by combining weighted gene co-expression network analysis (WGCNA) with machine learning algorithms. Among these, SOCS3 demonstrated robust diagnostic potential [19]. The study further constructed an artificial neural network model and validated its effectiveness in distinguishing patients from controls.

Regarding the integration of clinical variables, researchers are exploring the combination of electronic health record (EHR) data with molecular features to develop multimodal predictive models. For instance, one study performed model derivation and validation using EHR data from January 2016 to February 2020, followed by temporal validation from January 2021 to December 2022. The performance of machine learning algorithms was compared with logistic regression (specifically ridge regression and gradient tree boosting) in predicting the development of sepsis and septic shock [20]. These models not only incorporate traditional clinical risk factors (such as age, cardiovascular comorbidities, and inflammatory markers) but also integrate genomic risk scores, protein biomarkers, and electrocardiographic features, thereby offering a more comprehensive risk assessment. This approach may facilitate timely risk stratification, support data-driven clinical decision-making, and ultimately improve outcomes for sepsis patients [21].

DISCOVERY OF EMERGING THERAPEUTIC TARGETS

The integration of multi-omics and artificial intelligence has not only enhanced risk prediction capabilities but has also significantly advanced the discovery of novel therapeutic targets. Analysis based on transcriptomic data has revealed that the formation of neutrophil extracellular traps (NETs) plays a key role in sepsis-induced myocardial injury [22]. Experiments have demonstrated that inhibiting NET formation (using CI-amidine or Sivelestat) or degrading NET components (using DNase I) can reduce myocardial inflammation and apoptosis, thereby preserving cardiac contractile function [22–24]. This provides a promising new direction for treating sepsis-associated arrhythmias.

Immune checkpoint molecules have also emerged as potential targets. Studies indicate that in the context of sepsis-induced myocardial dysfunction, the expression of immune checkpoints such as programmed death-ligand 1 (PD-L1) is altered, and targeting these molecules may modulate the immune response and improve cardiac function [25]. Concurrently, excessive activation of the complement system, particularly the C5a–C5a receptor axis, has been shown to contribute to the pathological process of sepsis-induced myocardial injury [26,27]. Inhibitors targeting this pathway have demonstrated favorable effects in preclinical studies.

In the field of neuroimmune modulation, studies have confirmed that neuromodulation strategies such as electroacupuncture and non-invasive vagus nerve stimulation can mitigate cardiac damage by rebalancing neuro-immune interactions [28-30]. These findings provide a basis for developing non-pharmacological treatments for septic cardiac complications.

Notably, drug repositioning analysis has emerged as an effective approach for identifying therapeutic strategies. By screening interactions between FDA-approved drugs and key targets using artificial intelligence algorithms, studies have found that drugs such as dexamethasone, resveratrol, and curcumin may target SOCS3 [31-35], thereby exerting therapeutic effects. This approach substantially shortens the pathway from target discovery to clinical application, offering significant translational value.

LIMITATIONS

While research on the application of multi-omics and artificial intelligence (AI) in sepsis-associated atrial fibrillation (AF) has made progress, significant limitations remain in clinical translation.** The specific challenges are as follows: First, the integration of multi-omics is insufficiently deep. Most current studies are confined to single-omics analyses, lacking systematic cross-omics and multi-level integration. This makes it difficult to reveal causal relationships between different molecular layers. Furthermore, research designs are predominantly cross-sectional, lacking longitudinal dynamic monitoring, which limits the ability to establish causality within the pathological mechanisms. Additionally, molecular discrepancies between blood samples and atrial tissue hinder the accurate inference of intra-atrial pathological changes based on peripheral biomarkers.

Second, AI models face limitations in generalizability. They are often prone to overfitting due to small sample sizes and data bias, and most models lack independent external validation, thereby reducing their clinical reliability. Model development frequently prioritizes a data-driven approach, lacking mechanistic explanations and clinical insights, which impedes gaining clinical trust. Moreover, existing models are predominantly static predictors and cannot adapt to the dynamic progression of illness in sepsis patients.

Table 2: Integrated Analytical Framework and Anticipated Outputs Proposed in This Study

Analysis level	Research methods	Expected output	Innovative
Multidimensional data integration	Multi-omics data fusion and dynamic sampling design	Construct the molecular evolution map of atrial fibrillation in sepsis	Break through the limitations of a single time point and a single omics
Development of computational models	Graph neural networks, transfer learning, dynamic prediction	High-precision and interpretable clinical prediction models	Solve the problems of model generalization ability and clinical applicability
Mechanism verification	Organoid models, single-cell technology, gene editing	Verify the functions of candidate targets and intervention strategies	Establish a complete chain from computational discovery to experimental verification
Clinical transformation	Prospective cohort, adaptive clinical trial design	Individualized risk stratification and treatment plans	Promote the implementation of the concept of precision medicine in atrial fibrillation caused by sepsis

Third, the translation of targets and drug development faces its own set of challenges. Insufficient specificity of some targets may lead to off-target risks; for instance, while inhibiting NETosis might reduce inflammation, it could also compromise the host's defense against infection. Species differences and patient heterogeneity further complicate the translation of preclinical findings to humans. Additionally, the long-term safety of precision drug delivery systems, such as nanoparticles, requires further validation.

Looking ahead, future research should focus on constructing multi-level, dynamic frameworks that integrate multi-omics and AI analysis. This involves collecting longitudinal multi-omics data to build molecular regulatory networks and employing methods like Mendelian randomization to strengthen causal inference in target validation. Leveraging indirect tissue-specific inference to elucidate intra-atrial mechanisms, with a particular focus on the interplay between the immune and electrophysiological systems, combined with single-cell technologies to decipher cellular interaction networks, will be crucial for systematically advancing the establishment of a precision prevention and treatment framework for sepsis-associated AF (Table 2).

DEVELOPMENT OF A DYNAMIC RISK PREDICTION MODEL

In terms of model development, this study aims to construct a dynamic, interpretable, and clinically applicable risk prediction model. We will employ time-series analytical methods to incorporate continuously changing data on vital signs, laboratory tests, therapeutic interventions, and molecular biomarkers, thereby establishing a real-time early warning system for sepsis-associated atrial fibrillation (AF). Compared to static models, such a dynamic model can better capture the rapidly evolving clinical status of septic patients, providing more timely evidence for clinical intervention.

To address the issue of model interpretability, we will apply explainable artificial intelligence (XAI) techniques, such as SHAP and LIME, to clarify the contribution of each feature variable to the prediction outcome. This approach is designed to enhance clinicians' understanding of and trust in the model. Furthermore, we will develop a multi-task learning framework, enabling the model to simultaneously predict multiple clinical endpoints (e.g., occurrence of AF, shock, death), thereby better supporting complex clinical decision-making needs.

To improve the model's generalizability, we will utilize privacy-preserving computing techniques, such as federated learning, to train the model on multi-center data without sharing the raw datasets. This strategy will effectively mitigate bias inherent in single-center data and accelerate the deployment of the model in real-world clinical settings.

For target identification, a network medicine strategy will be adopted to screen key nodes within molecular networks as potential therapeutic targets. This approach aims to enhance target stability and reduce off-target risks. In drug development, AI will be leveraged to analyze interactions between approved drugs and disease targets, facilitating the rapid screening of candidates for drug repurposing, which can significantly shorten the development timeline. Additionally, we will explore the modification of patient-derived exosomes to serve as a delivery system, enabling the targeted transport of therapeutic molecules (e.g., microRNA-223) to cardiomyocytes to achieve precise and low-toxicity treatment.

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