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Original Article

# Clinical Utility of AI-Integrated Metabolomic and Proteomic Signatures for Guiding Early Antibiotic Therapy in Sepsis

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## ABSTRACT

*Background: Rapid selection of appropriate antimicrobial therapy in sepsis is limited by diagnostic uncertainty during the early hours of critical illness. Artificial intelligence-assisted integration of metabolomic and proteomic data may provide earlier biologically informed decision support. Objective: To evaluate whether AI-guided multi-omic diagnostics improve the timeliness of appropriate antimicrobial therapy compared with standard care in sepsis. Methods: This single-center parallel-group randomized controlled trial enrolled 96 adults with sepsis and allocated 48 participants per group. Ninety participants had evaluable outcome data. The intervention combined rapid metabolomic and proteomic profiling with AI-assisted clinical decision support. The primary outcomes were appropriate targeted therapy within 12 hours and time to appropriate treatment. Results: Appropriate therapy within 12 hours was achieved in 37/45 (82.2%) intervention participants versus 20/45 (44.4%) controls (RR 1.85, 95% CI 1.30–2.64; p<0.001). Mean time to appropriate therapy was 5.8 versus 14.2 hours. SOFA scores decreased from 8.3 ± 2.0 to 3.1 ± 1.4 versus 8.5 ± 2.2 to 5.4 ± 1.8, with a significant group-by-time interaction (p<0.001). ICU stay was 7.2 versus 10.5 days, while 28-day mortality was 13.3% versus 31.1%. Conclusion: AI-guided multi-omic decision support improved early appropriate antimicrobial treatment and was associated with more favorable clinical trajectories. Keywords: Artificial Intelligence, Antimicrobial Therapy, Metabolomics, Precision Medicine, Proteomics, Sepsis.*

## INTRODUCTION

Sepsis is a life-threatening syndrome characterized by acute organ dysfunction resulting from a dysregulated host response to infection and remains a major cause of critical illness and mortality worldwide (1,2). Its biological and clinical heterogeneity contributes substantially to difficulties in early recognition, prognostic stratification, and individualized treatment (3,4). Contemporary management therefore prioritizes rapid clinical recognition, hemodynamic stabilization, source control, and timely administration of effective antimicrobial therapy while simultaneously attempting to minimize unnecessary exposure to broad-spectrum agents (5).

The timing and appropriateness of antimicrobial treatment are particularly important in severe infection. Delayed administration of active antimicrobial therapy has repeatedly been associated with adverse outcomes in critically

ill patients, although the magnitude of this association varies according to disease severity, infection source, and the time threshold evaluated (6,7). In a large bloodstream-infection cohort, inappropriate antimicrobial treatment persisting beyond approximately 12 hours was associated with increased 30-day mortality, supporting the clinical relevance of rapid pathogen-directed therapeutic optimization (8). Appropriate empirical antimicrobial therapy has similarly been associated with lower mortality among patients with bloodstream infections, particularly when resistant organisms complicate initial therapeutic selection (9). These findings support a clinical strategy that combines sufficiently early empirical coverage with rapid reassessment and targeted adjustment rather than indiscriminate continuation of broad-spectrum therapy.

Achieving this balance remains difficult because conventional diagnostic approaches frequently provide incomplete information during the earliest hours of sepsis management. Clinical manifestations of infection overlap with those of sterile inflammatory states, while commonly used biomarkers such as C-reactive protein and procalcitonin lack sufficient specificity to independently establish an infectious etiology or identify an optimal antimicrobial regimen (10,11). Conventional blood culture remains central to microbiological diagnosis and antimicrobial susceptibility testing, but pathogen recovery is incomplete and definitive identification and susceptibility information may not become available within the timeframe required for initial therapeutic decision-making (12). Consequently, empirical broad-spectrum antimicrobial treatment remains common even when the responsible pathogen and susceptibility profile are uncertain.

Rapid microbiological diagnostics have increasingly been evaluated as a means of narrowing this therapeutic information gap. Molecular pathogen-detection systems, rapid phenotypic susceptibility platforms, direct-from-blood assays, mass-spectrometry-based approaches, and emerging culture-independent technologies can substantially reduce diagnostic turnaround time compared with conventional workflows (12,13). Importantly, their clinical value appears greatest when diagnostic information is integrated with active antimicrobial-stewardship intervention rather than delivered in isolation. A recent network meta-analysis involving more than 25,000 bloodstream-infection encounters found that rapid diagnostic testing combined with antimicrobial stewardship reduced time to optimal therapy and was associated with improved clinical outcomes compared with conventional culture-based strategies alone (14). These observations provide a strong rationale for evaluating diagnostic systems according to their capacity to alter clinically meaningful treatment decisions rather than analytical accuracy alone.

Parallel advances in systems biology have revealed that sepsis is characterized by extensive molecular heterogeneity involving immune dysregulation, endothelial injury, coagulation abnormalities, mitochondrial dysfunction, metabolic reprogramming, and organ-specific responses (3,15). This heterogeneity limits the ability of single circulating biomarkers to capture the biological complexity of the syndrome and has accelerated interest in high-dimensional molecular phenotyping and precision-medicine approaches (4,15). Proteomic and metabolomic profiling are particularly relevant because proteins reflect dynamic host inflammatory and immune signaling, whereas metabolites represent downstream functional changes in cellular energetics, amino-acid metabolism, oxidative stress, and host-pathogen interactions (16).

Integrated metabolomic and proteomic studies have demonstrated that patients with sepsis exhibit reproducible alterations across multiple biological pathways. Chen et al. identified broad disturbances in amino-acid metabolism and inflammatory pathways through combined serum metabolomic and proteomic analysis, with several metabolites demonstrating diagnostic discrimination in validation datasets (16). Metabolomics combined with machine-learning techniques has subsequently identified panels of differentially expressed metabolites associated with sepsis diagnosis and prognosis, illustrating the potential value of computationally assisted molecular signatures (17). More recent studies have further demonstrated early metabolic remodeling preceding or accompanying clinical sepsis and have linked systemic metabolic abnormalities with mitochondrial and organ-specific dysfunction (18). Proteomic research has likewise identified candidate blood-based signatures capable of distinguishing sepsis from comparator populations and reflecting disease severity, although independent clinical validation remains essential before such signatures can be used routinely (19).

The clinical appeal of multi-omic profiling lies in its ability to integrate complementary biological information across multiple molecular levels rather than relying on isolated biomarkers. Contemporary precision-sepsis research increasingly conceptualizes the syndrome as a collection of molecularly and clinically distinguishable endotypes

that may differ in pathophysiology, prognosis, and treatment response (3,4,15). Machine-learning and artificial-intelligence methods are particularly suited to this setting because they can process high-dimensional, nonlinear relationships among molecular and clinical variables, identify latent patterns, and generate individualized predictions that are difficult to derive through conventional bedside assessment alone (20).

Artificial intelligence has therefore been investigated across multiple stages of sepsis care, including early detection, diagnostic classification, prognostic prediction, subphenotyping, antimicrobial selection, and clinical decision support (20,21). Prospective implementation studies of machine-learning sepsis-alert systems have suggested that rapid clinician interaction with algorithmic alerts may be associated with earlier treatment and improved clinical outcomes, demonstrating that computational models can influence actual care pathways when embedded within clinical workflows (22). However, performance remains heterogeneous, and concerns persist regarding false-positive alerts, model calibration, explainability, external validation, dataset shift, algorithmic bias, and the generalizability of models developed within individual healthcare systems (21).

The convergence of artificial intelligence with multi-omic profiling represents a particularly promising but incompletely validated extension of this precision-medicine framework. Recent reviews describe increasing integration of genomics, transcriptomics, proteomics, metabolomics, microbiome information, and clinical data to identify sepsis phenotypes and generate predictive models (20,21). Nevertheless, most studies remain focused on biomarker discovery, biological classification, retrospective prediction, or diagnostic discrimination rather than prospective demonstration that AI-integrated multi-omic information can meaningfully improve antimicrobial decision-making at the bedside. Recent analyses therefore continue to emphasize the need for standardized datasets, external validation, explainable algorithms, prospective interventional studies, and patient-centered clinical endpoints before AI-driven multi-omics can be considered ready for routine implementation (20,21).

This translational gap is especially important because diagnostic accuracy does not necessarily translate into therapeutic effectiveness. A clinically useful sepsis diagnostic platform must generate interpretable information rapidly enough to alter antimicrobial treatment during the narrow period in which empirical therapy is being selected and refined. Evidence from rapid diagnostic and antimicrobial-stewardship studies suggests that reductions in diagnostic turnaround time can improve time to optimal therapy when results are actively incorporated into prescribing decisions (13,14). Whether high-dimensional metabolomic and proteomic signatures processed through artificial intelligence can provide comparable or additional benefit requires prospective evaluation.

The present randomized controlled trial was therefore designed to evaluate the clinical utility of an artificial intelligence-guided diagnostic strategy integrating metabolomic and proteomic signatures in patients with sepsis. The primary objective was to determine whether AI-guided multi-omic decision support increased the proportion of patients receiving appropriate targeted antimicrobial therapy within 12 hours and reduced the time to initiation of appropriate therapy compared with standard clinical care. Secondary objectives were to compare trajectories of Sequential Organ Failure Assessment (SOFA) scores, time to clinical stabilization, intensive care unit length of stay, and 28-day all-cause mortality between treatment groups. The study hypothesis was that incorporation of rapidly generated multi-omic decision support into early sepsis management would facilitate more timely appropriate antimicrobial treatment and be accompanied by more favorable subsequent clinical outcomes.

## MATERIALS AND METHODS

This prospective, single-center, parallel-group randomized controlled trial was conducted in the intensive care units of a tertiary referral center in the Islamabad–Rawalpindi region of Pakistan between May and December 2025, representing a total study period of eight months. Adult patients presenting through the emergency department or intensive care service with suspected infection and sepsis were screened for eligibility. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) as life-threatening organ dysfunction caused by a dysregulated host response to infection, operationalized clinically by an acute increase of at least two points in the SOFA score attributable to infection (1).

A total of 96 eligible adults were enrolled within three hours of emergency department or intensive care admission. Participants were required to be aged 18 years or older and to meet the clinical criteria for sepsis. Exclusion criteria included severe neutropenia, pregnancy, advanced terminal illness associated with active limitation of goals of

care, and receipt of broad-spectrum antimicrobial therapy for more than 12 hours before enrollment. Eligible participants were randomly allocated in a 1:1 ratio to the AI-guided multi-omic intervention group (n=48) or the standard-care control group (n=48).

Random allocation was performed using a computer-generated block-randomization sequence with variable block sizes. Allocation concealment was maintained through sequentially numbered, opaque, sealed envelopes administered independently from the treating clinical team. Blinding of treating physicians was not feasible because clinicians allocated to the intervention arm were required to receive and incorporate the AI-generated diagnostic information into therapeutic decisions. Outcome assessors, laboratory personnel, and personnel responsible for statistical analysis remained unaware of treatment allocation to minimize ascertainment and analytical bias.

Participants in both study groups received immediate stabilization and empirical antimicrobial treatment according to established contemporary principles of sepsis management, including prompt recognition, infection-directed therapy, physiological support, and reassessment of antimicrobial treatment as additional diagnostic information became available (5,6). In the standard-care group, antimicrobial selection, continuation, escalation, modification, and de-escalation were based on routine clinical evaluation, serial laboratory findings, inflammatory biomarkers including C-reactive protein and procalcitonin, microbiological culture results, and conventional antimicrobial susceptibility testing. This approach reflected standard diagnostic pathways in which empirical treatment is progressively refined as microbiological and clinical information becomes available (10–13).

Participants allocated to the AI-guided intervention underwent peripheral blood collection at enrollment for rapid molecular profiling in addition to standard clinical investigations. Metabolomic profiling was performed using high-performance liquid chromatography coupled with mass spectrometry, whereas targeted proteomic assessment used tandem-mass-tag-based analytical procedures. The rationale for combining these molecular domains was based on evidence that metabolomic and proteomic alterations capture complementary components of the host response to sepsis, including inflammatory signaling, immune activation, metabolic reprogramming, amino-acid metabolism, cellular energetics, and organ dysfunction (15–19).

The resulting high-dimensional molecular information was processed through the study machine-learning algorithm to generate an individualized diagnostic report. The report summarized the algorithm-estimated probability of bacterial sepsis, the host metabolic-response profile, and algorithm-derived antimicrobial susceptibility predictions intended to support clinical therapeutic decisions. The diagnostic output was made available to the clinical team within approximately four hours of sample collection. Artificial-intelligence-based integration was used because conventional analytical methods may be insufficient to model complex nonlinear relationships across high-dimensional molecular datasets, whereas machine-learning approaches can combine multiple molecular features into clinically interpretable predictive outputs (20,21).

Treating clinicians in the intervention arm interpreted the AI-generated report alongside bedside clinical assessment, routine biochemical measurements, microbiological findings, inflammatory markers, and conventional susceptibility information. Antimicrobial treatment could subsequently be continued, modified, escalated, narrowed, or discontinued according to the integrated clinical assessment. Therapeutic decisions were reassessed twice daily during the active intervention period. This strategy was consistent with the broader principle that rapid diagnostic technologies exert their greatest clinical effect when diagnostic information is actively incorporated into antimicrobial optimization rather than presented independently from prescribing decisions (13,14).

The primary clinical outcome was the proportion of patients receiving appropriate targeted antimicrobial therapy within 12 hours of presentation. Appropriate therapy was defined according to concordance between the prescribed antimicrobial regimen and the ultimately identified or clinically adjudicated infectious process, incorporating available microbiological and antimicrobial-susceptibility information. The complementary primary endpoint was elapsed time from presentation to initiation of appropriate antimicrobial therapy, expressed in hours. Selection of a time-sensitive endpoint was supported by evidence demonstrating that prolonged inappropriate antimicrobial treatment in severe infection and bloodstream infection is associated with poorer outcomes and that rapid diagnostic interventions can substantially shorten time to optimized treatment (6–9,14).

Secondary outcomes included SOFA score trajectory, time to clinical stabilization, intensive care unit length of stay, and 28-day all-cause mortality. SOFA scores were determined at baseline, Day 3, and Day 7 to quantify temporal changes in organ dysfunction. The SOFA framework incorporates respiratory, coagulation, hepatic, cardiovascular, neurological, and renal dysfunction and remains central to clinical characterization of sepsis-associated organ failure (1). Intensive care unit length of stay and time to stabilization were recorded in days, whereas vital status was assessed through 28 days following enrollment.

Of the 96 randomized participants, complete outcome data were available for 90 participants, comprising 45 participants in each treatment group. Six randomized participants did not contribute complete endpoint data because of withdrawal of consent, transfer to an external facility, or unavailable follow-up information. The reported outcome analyses were therefore based on participants with evaluable endpoint data. The final 90-participant analysis was treated as an available-case analysis rather than being described as a conventional intention-to-treat analysis, because participants without evaluable outcomes were not included in the reported final comparisons.

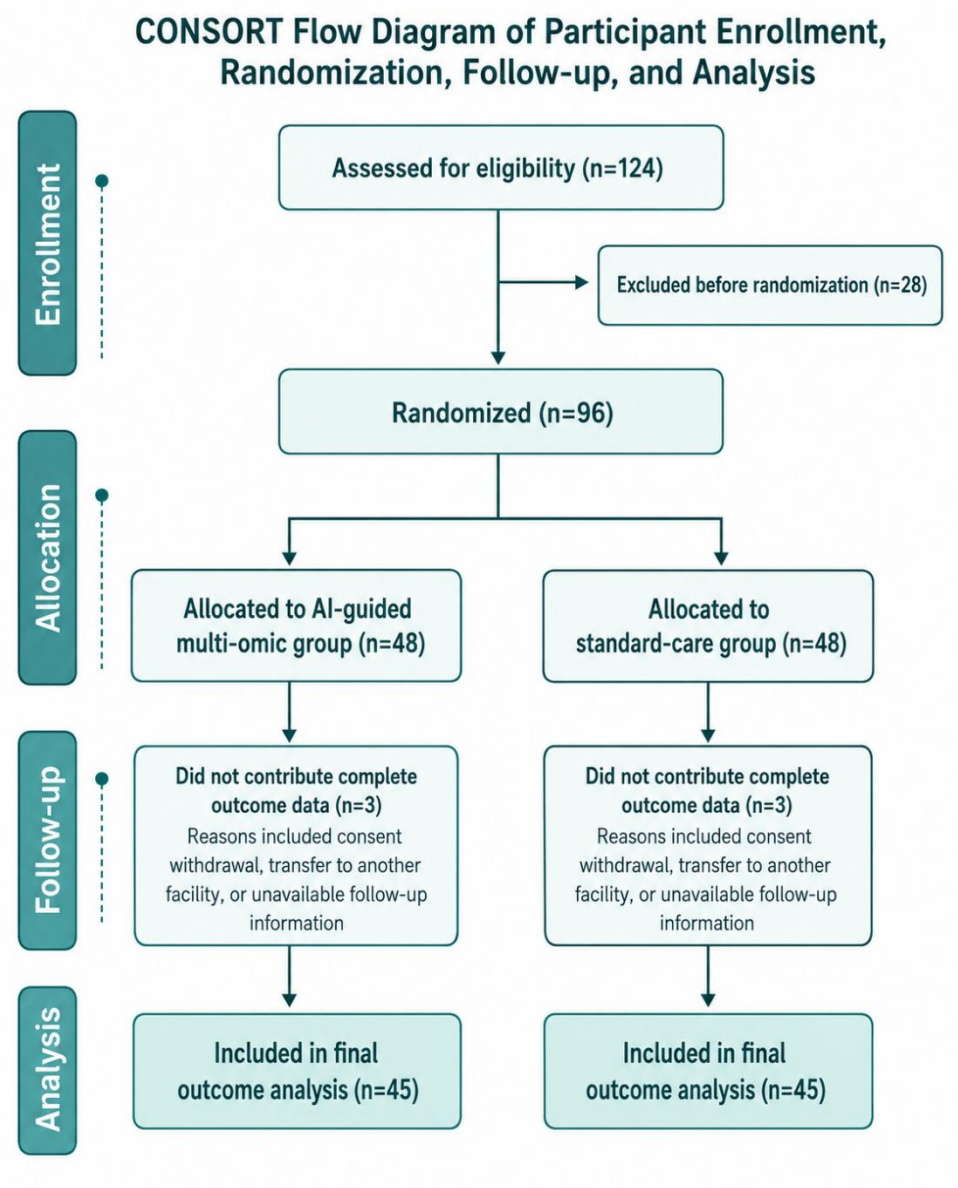


*Figure 1 CONSORT Flowchart*

Continuous variables were summarized as mean ± standard deviation when their distributions were compatible with parametric analysis, whereas categorical variables were summarized as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro–Wilk test. Baseline characteristics were summarized descriptively to evaluate the distribution of demographic and clinical characteristics following randomization;

absence of statistically significant baseline differences was not interpreted as proof of treatment-group equivalence.

For the binary primary endpoint of appropriate targeted antimicrobial therapy within 12 hours, treatment groups were compared using Pearson's chi-square test or Fisher's exact test when expected cell frequencies did not satisfy chi-square assumptions. Treatment effects were expressed using absolute risk differences and relative measures of effect with 95% confidence intervals where derivable from the available data. This approach replaced the use of an independent-samples t-test for the binary primary endpoint, because categorical response proportions require categorical rather than continuous-outcome statistical procedures.

Continuous between-group outcomes, including time to appropriate antimicrobial treatment, time to clinical stabilization, and intensive care unit length of stay, were evaluated using independent-samples t-tests when parametric assumptions were satisfied. Within-group changes in SOFA score between assessment timepoints were examined using paired-samples t-tests. Longitudinal SOFA trajectories across baseline, Day 3, and Day 7 were evaluated using repeated-measures analysis of variance, with time treated as the within-participant factor and treatment allocation as the between-participant factor. The group-by-time interaction represented the principal inferential test of whether the trajectory of organ-dysfunction recovery differed between the AI-guided and standard-care groups.

Time from presentation to initiation of appropriate antimicrobial therapy was additionally evaluated as a time-to-event endpoint using Kaplan–Meier methodology. Because the event of interest was initiation of appropriate antimicrobial therapy rather than remaining untreated, the graphical presentation displayed cumulative event probability corresponding to one minus the Kaplan–Meier survival function. Participants who had not initiated appropriate therapy during the observed interval contributed event-free follow-up through their last evaluable timepoint. Curves were compared between treatment groups using the log-rank test. The analysis covered the first 24 hours following presentation and included the clinically important 12-hour assessment point.

Twenty-eight-day all-cause mortality was analyzed as a categorical outcome using an appropriate test of proportions, with absolute and relative treatment-effect measures and 95% confidence intervals reported where supported by the available data. Pearson correlation analysis was used for exploratory examination of the relationship between time to appropriate antimicrobial therapy and subsequent change in SOFA score when assumptions for parametric correlation were satisfied. Statistical testing was two-sided, with statistical significance defined as $p<0.05$.

## RESULTS

A total of 124 patients were assessed for eligibility during the eight-month study period. Ninety-six participants met the eligibility criteria and were randomized equally to the AI-guided multi-omic intervention group (n=48) or standard-care control group (n=48). During follow-up, three participants in each group did not contribute complete outcome data because of consent withdrawal, transfer to another facility, or unavailable follow-up information. Consequently, 90 participants, comprising 45 in each treatment group, were included in the available-case outcome analyses.

*Table 1. Participant Flow and Analysis Population*

| Study stage | AI-guided multi-omic group, n | Standard-care group, n | Total, n |
|---|---|---|---|
| **Assessed for eligibility** | — | — | 124 |
| **Randomized** | 48 | 48 | 96 |
| **Did not contribute complete outcome data** | 3 | 3 | 6 |
| **Included in final outcome analysis** | 45 | 45 | 90 |

The primary endpoint demonstrated a marked difference between groups. Appropriate targeted antimicrobial therapy was initiated within 12 hours in 37 of 45 participants (82.2%) in the AI-guided group compared with 20 of 45 (44.4%) in the standard-care group. The absolute increase was 37.8 percentage points (95% CI 19.5–56.1), corresponding to a relative risk of 1.85 (95% CI 1.30–2.64). Mean time to appropriate antimicrobial treatment was also substantially shorter with AI-guided care, at 5.8 hours compared with 14.2 hours under standard care, representing an observed between-group difference of 8.4 hours.

*Table 2. Primary Antimicrobial-Therapy Outcomes*

| Outcome | AI-guided multi-omic group (n=45) | Standard-care group (n=45) | Effect estimate | 95% CI | p-value |
|---|---|---|---|---|---|
| **Appropriate therapy within 12 h, n (%)** | 37 (82.2) | 20 (44.4) | Risk difference, 37.8 percentage points | 19.5 to 56.1 | <0.001 |
| **Appropriate therapy within 12 h** | 37/45 | 20/45 | RR, 1.85 | 1.30 to 2.64 | <0.001 |
| **Time to appropriate therapy, h** | 5.8 | 14.2 | Mean difference, −8.4 h | — | <0.001 |

RR, relative risk. Confidence intervals for the binary primary outcome were derived from the reported group counts.

Organ dysfunction decreased over time in both groups but declined more markedly among participants receiving AI-guided multi-omic care. Mean SOFA score decreased from 8.3 ± 2.0 at baseline to 3.1 ± 1.4 on Day 7 in the intervention group, an observed reduction of 5.2 points. In the standard-care group, mean SOFA score decreased from 8.5 ± 2.2 to 5.4 ± 1.8, corresponding to a reduction of 3.1 points. The reported repeated-measures analysis demonstrated a significant group-by-time interaction, $F(2,176)=18.62$, $p<0.001$, indicating different SOFA trajectories between treatment groups.

*Table 3. Change in SOFA Score From Baseline to Day 7*

| Outcome | AI-guided multi-omic group (n=45) | Standard-care group (n=45) |
|---|---|---|
| **Baseline SOFA score, mean ± SD** | 8.3 ± 2.0 | 8.5 ± 2.2 |
| **Day 7 SOFA score, mean ± SD** | 3.1 ± 1.4 | 5.4 ± 1.8 |
| **Observed mean change, points** | −5.2 | −3.1 |

Repeated-measures group × time interaction: $F(2,176)=18.62$, $p<0.001$.

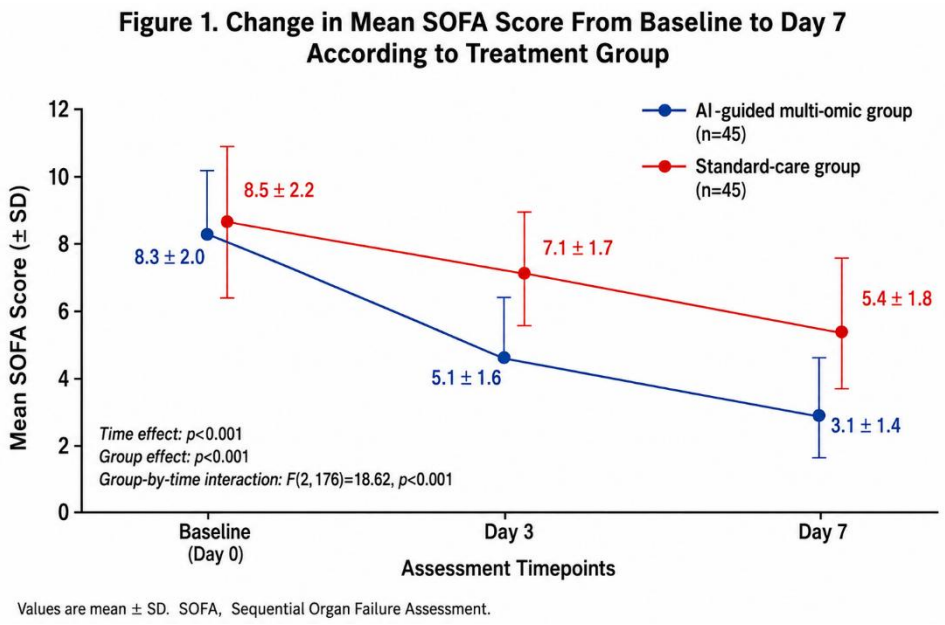


*Figure 1. Change in Mean SOFA Score From Baseline to Day 7 According to Treatment Group. Mean SOFA scores declined from 8.3 ± 2.0 at baseline to 3.1 ± 1.4 at Day 7 in the AI-guided multi-omic group and from 8.5 ± 2.2 to 5.4 ± 1.8 in the standard-care group. The group-by-time interaction was statistically significant, $F(2,176)=18.62$, $p<0.001$, demonstrating a greater reduction in organ dysfunction over time in the intervention group.*

*Table 4. Secondary Clinical Outcomes*

| Outcome | AI-guided multi-omic group (n=45) | Standard-care group (n=45) | Between-group effect | p-value |
|---|---|---|---|---|
| **ICU length of stay, days** | 7.2 | 10.5 | −3.3 days | <0.001 |
| **Time to clinical stabilization, days** | 3.4 | 5.8 | −2.4 days | <0.001 |
| **28-day all-cause mortality, n (%)** | 6 (13.3) | 14 (31.1) | −17.8 percentage points | 0.046 |
| **28-day mortality, relative risk** | — | — | 0.43 | — |

Secondary clinical outcomes also favored the AI-guided group. Mean ICU length of stay was 7.2 days in the intervention group compared with 10.5 days in controls, an observed difference of 3.3 days. Mean time to clinical stabilization was 3.4 versus 5.8 days, respectively, representing an observed difference of 2.4 days. Twenty-eight-day all-cause mortality occurred in 6 of 45 participants (13.3%) receiving AI-guided care and 14 of 45 (31.1%) receiving standard care. This corresponded to an absolute risk difference of −17.8 percentage points and a relative risk of approximately 0.43. Because the study was modest in size, the mortality estimate should be interpreted as a secondary outcome rather than definitive evidence of a survival effect.

The cumulative time-to-event analysis further demonstrated earlier initiation of appropriate antimicrobial therapy in the intervention group. By 12 hours, the cumulative proportion receiving appropriate therapy was 82.2% compared with 44.4% in the standard-care group, and the reported log-rank comparison was p<0.001. This result was concordant with the binary 12-hour primary endpoint and the shorter mean time to appropriate treatment.

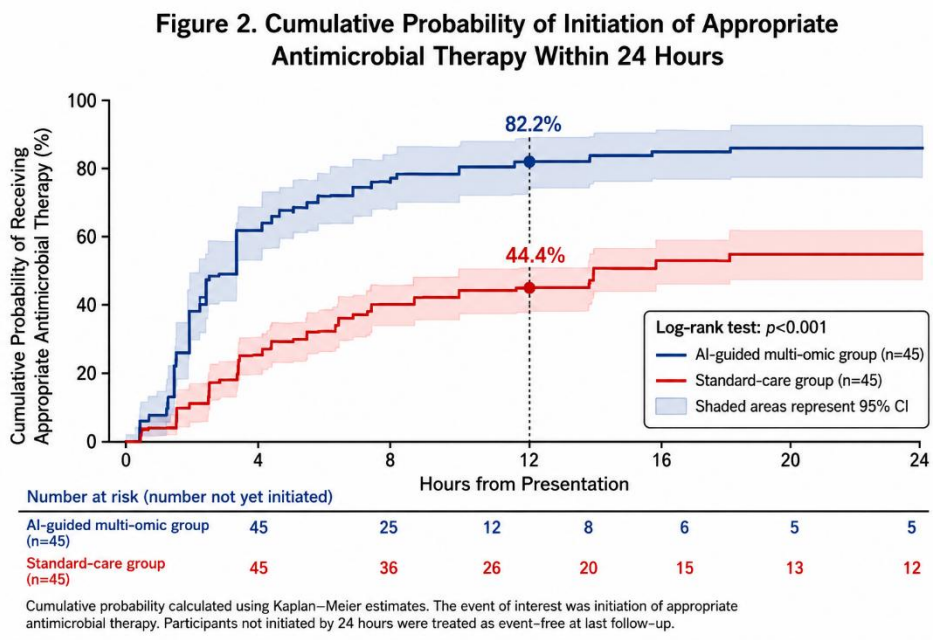


*Figure 2. Cumulative Probability of Initiation of Appropriate Antimicrobial Therapy Within 24 Hours. The cumulative probability of receiving appropriate antimicrobial therapy increased more rapidly in the AI-guided multi-omic group than in the standard-care group. At 12 hours, 82.2% of intervention participants compared with 44.4% of controls had received appropriate therapy, and the cumulative curves differed significantly by log-rank testing (p<0.001).*

## DISCUSSION

This randomized controlled trial found that integration of an AI-guided metabolomic and proteomic decision-support strategy into early sepsis management was associated with substantially more rapid delivery of appropriate antimicrobial therapy than standard clinical care. More than four-fifths of participants receiving AI-guided care had received appropriate targeted treatment within 12 hours compared with fewer than half of controls, while mean time to appropriate treatment was reduced by more than eight hours. These differences were accompanied by a greater improvement in SOFA score over seven days, shorter time to clinical stabilization and ICU stay, and a lower observed 28-day mortality. The principal contribution of the study is therefore not merely demonstration of molecular discrimination, but prospective evidence that rapidly generated high-dimensional biological information can potentially influence time-sensitive bedside antimicrobial decisions.

The magnitude of improvement in early appropriate therapy is clinically relevant because both timing and appropriateness of antimicrobial treatment are central determinants of outcome in severe infection. Contemporary evidence indicates that delays in active treatment are particularly consequential in patients with severe sepsis, septic shock, and bloodstream infection, although the relationship is influenced by baseline severity and the interval used to define delay (6–9). Van Heuverswyn et al. found that inappropriate therapy persisting at 12 hours was associated with increased 30-day mortality in a large bloodstream-infection cohort (8), while Ohnuma et al. reported an association between appropriate initial empirical treatment and lower in-hospital mortality across more than 32,000 bloodstream infections (9). The present difference of 82.2% versus 44.4% appropriate therapy by 12 hours is therefore directionally consistent with the broader evidence supporting rapid antimicrobial optimization rather than prolonged diagnostic uncertainty.

These results also align with evidence that rapid diagnostics have their greatest clinical value when the information generated is actively linked to therapeutic decision-making. A recent systematic review and network meta-analysis showed that rapid diagnostic testing combined with antimicrobial stewardship shortened time to optimal therapy and was associated with more favorable outcomes than conventional culture-based pathways alone (14). The current study extends this principle beyond direct pathogen-identification technologies by using host metabolomic

and proteomic information interpreted through an AI algorithm. However, the comparison should be made cautiously because molecular host-response profiling and conventional rapid microbiological diagnostics measure different biological domains. The findings therefore support complementarity rather than replacement of culture, susceptibility testing, and established rapid pathogen-detection platforms.

The observed SOFA trajectory provides additional evidence that the intervention was associated with differences beyond prescribing behavior. Mean SOFA score fell by 5.2 points in the AI-guided group compared with 3.1 points under standard care, and the significant group-by-time interaction suggested a more favorable trajectory of organ dysfunction. This is biologically plausible because delayed control of infection may prolong inflammatory, endothelial, metabolic, and microcirculatory disturbances that contribute to progressive organ injury. Contemporary sepsis research increasingly emphasizes that organ dysfunction emerges from interacting immune, metabolic, endothelial, coagulation, and mitochondrial pathways rather than from a single linear inflammatory cascade (3,4,15). Consequently, earlier delivery of microbiologically appropriate treatment could plausibly reduce the duration of the infectious stimulus while supportive care addresses the resulting physiological dysfunction.

The mechanistic rationale for combining metabolomic and proteomic information is supported by a growing body of translational evidence. Póvoa et al. highlighted the capacity of proteomics and metabolomics to generate multidimensional diagnostic and prognostic signatures in severe infection, while also noting that routine clinical implementation remains limited (23). Chen et al. demonstrated widespread disturbances of amino-acid metabolism and inflammatory pathways in patients with sepsis using integrated proteomic and metabolomic analysis (16). More recently, high-throughput plasma proteomics in more than 1,600 patients has demonstrated substantial heterogeneity in host-response states and identified molecular patterns associated with infection etiology, organ failure, severity, and outcome (24). These findings provide biological support for the premise that simultaneous molecular profiling may contain clinically useful information not captured by conventional inflammatory biomarkers alone.

The present findings are also relevant to the evolving concept of sepsis endotyping. Increasing evidence indicates that patients meeting the same clinical definition of sepsis can exhibit markedly different immune, metabolic, endothelial, and transcriptomic states, with potentially different prognoses and therapeutic responses (3,4,15). Antcliffe et al. emphasized that clinically actionable subphenotypes may ultimately allow treatment to be matched to treatable biological traits rather than applied uniformly across a heterogeneous syndrome (25). Recent multicenter work integrating longitudinal transcriptomic, proteomic, metabolomic, and phenomic data has further demonstrated that multi-omic subgrouping can identify patient strata associated with differential treatment responses, illustrating the potential future role of biologically informed therapeutic stratification (26). The intervention evaluated here should therefore be viewed within a broader movement toward dynamic precision phenotyping rather than as an isolated diagnostic assay.

Artificial intelligence provides a practical computational framework for this approach because manually interpreting thousands of interacting molecular measurements within a clinically meaningful timeframe is unrealistic. Existing AI applications in sepsis range from early-warning systems and risk prediction to subphenotyping, antimicrobial-support algorithms, and dynamic treatment modeling (20–22). Prospective evaluation of the TREWS machine-learning early-warning system previously demonstrated that timely clinician interaction with algorithmic alerts was associated with reduced mortality, organ failure, and length of stay, supporting the principle that AI may be most useful when tightly integrated into clinical workflow rather than functioning as a detached predictive model (22). More recent reviews similarly conclude that AI can enhance early recognition and individualized treatment but emphasize that clinical effectiveness depends on data quality, external validation, usability, and clinician engagement (27).

The reduction in ICU length of stay from 10.5 to 7.2 days and in time to clinical stabilization from 5.8 to 3.4 days may reflect the cumulative consequences of earlier effective antimicrobial treatment and faster control of the infectious process. Rapid-diagnostic literature similarly suggests that accelerated transition to optimal therapy can reduce unnecessary exposure to broad-spectrum antimicrobials and potentially shorten hospitalization when incorporated within effective stewardship programs (12–14). These outcomes are also important from a health-system perspective because prolonged ICU occupancy represents a major component of sepsis-related resource utilization. Nevertheless, formal economic evaluation was not performed in this study, and shorter ICU stay should

not be assumed to offset the acquisition, laboratory, informatics, and personnel costs required for rapid multi-omic profiling.

The observed difference in 28-day mortality, 13.3% versus 31.1%, is clinically notable but should be interpreted more cautiously than the primary antimicrobial endpoint. Mortality was a secondary outcome, only 20 deaths occurred overall, and the study was not primarily powered to establish a survival benefit. The point estimate suggests a potentially important treatment effect, but the modest sample size results in substantial statistical uncertainty. Larger multicenter trials are therefore required before concluding that AI-integrated multi-omic guidance reduces mortality. This cautious interpretation is consistent with recent reviews of AI-supported sepsis care, which report encouraging clinical signals but emphasize that many models remain inadequately externally validated and that evidence for direct patient-outcome improvement is still comparatively limited (21,27,28).

The difference between analytical performance and real-world clinical effectiveness is especially important for multi-omic systems. Recent reviews of omics-based sepsis diagnostics describe major advances in genomics, transcriptomics, proteomics, and metabolomics, but also identify persistent barriers including inter-platform variability, pre-analytical complexity, high cost, time-sensitive sample processing, data harmonization, and uncertain transportability across populations (28). Similarly, AI-focused reviews have highlighted risks arising from dataset shift, algorithmic bias, opaque prediction mechanisms, automation bias, and inadequate external validation (27). These issues are directly relevant to the current trial because a diagnostic algorithm developed or optimized in one setting may not preserve its calibration or clinical utility across centers with different pathogen ecology, antimicrobial-resistance patterns, patient demographics, or laboratory infrastructure.

Recent proteomic research reinforces both the promise and the complexity of this approach. Large-scale high-throughput mass-spectrometry studies have shown that the sepsis plasma proteome can stratify host-response states and identify features related to severity and outcome (24). Prospective multicenter proteomic work has also identified molecular subtypes with distinct clinical and immune characteristics and demonstrated that machine-learning classifiers may assign individuals to these states using reduced biomarker panels (29). Such developments support the feasibility of moving from discovery-scale omics toward smaller deployable signatures. However, their clinical usefulness ultimately depends on whether molecular classification changes therapeutic decisions and improves patient-centered outcomes, precisely the translational question addressed by the present study.

The study has several strengths. Its randomized parallel-group design provides stronger evidence regarding clinical utility than retrospective algorithm-development studies. The intervention was embedded within actual antimicrobial decision-making, a clinically meaningful 12-hour primary endpoint was used, organ dysfunction was assessed longitudinally, and outcome assessment extended to 28 days. The use of both metabolomic and proteomic information also reflects the multidimensional biology of sepsis more appropriately than reliance on a single inflammatory biomarker. In addition, the concordance between the categorical 12-hour endpoint, time-to-treatment analysis, SOFA trajectory, and resource-use outcomes provides a coherent pattern of clinical response.

Several limitations nevertheless require consideration. First, the study was conducted at a single tertiary center with a modest sample size, limiting external generalizability and the precision of secondary outcomes, particularly mortality. Second, six randomized participants were not included in the final outcome analysis; therefore, the reported analysis should be regarded as an available-case analysis rather than a strict intention-to-treat analysis. Third, clinicians could not be blinded to the intervention, creating the possibility of performance bias and more intensive therapeutic attention in the AI-guided group. Fourth, detailed external-validation metrics, calibration characteristics, decision thresholds, and explainability features of the machine-learning algorithm require fuller reporting to support reproducibility. Fifth, the ability to generate multi-omic results within approximately four hours depends on laboratory and computational infrastructure that may not be available in many hospitals.

Additional concerns relate to microbiological and implementation validity. Local pathogen prevalence and antimicrobial-resistance patterns may materially affect algorithm performance, making geographic external validation essential. The intervention also combined an algorithmic report with clinician interpretation; consequently, the observed effect represents the performance of the entire AI-assisted clinical pathway rather than the isolated accuracy of the algorithm itself. This distinction is important because the success of clinical AI systems depends not only on discrimination but also on workflow integration, user trust, interpretability, and the

quality of actions triggered by the output (22,27). Future studies should therefore evaluate both algorithmic metrics and implementation outcomes.

Future research should prioritize prospectively registered multicenter randomized trials involving heterogeneous populations and healthcare environments. These studies should report prespecified algorithm architecture, training and validation datasets, calibration, discrimination, decision thresholds, missing-data handling, and subgroup performance. Comparative-effectiveness designs could determine whether AI-integrated multi-omics provides incremental benefit beyond established rapid pathogen-identification and susceptibility platforms. Health-economic analyses should evaluate laboratory costs, antibiotic utilization, ICU bed-days, downstream complications, and implementation requirements. Emerging multi-omic frameworks integrating longitudinal biological data across multiple hospitals suggest that such precision approaches are increasingly technically feasible, but rigorous prospective validation remains the critical step before broad adoption (26,30).

## CONCLUSION

AI-guided integration of metabolomic and proteomic signatures was associated with substantially earlier initiation of appropriate targeted antimicrobial therapy than standard clinical care in this randomized trial, together with a more favorable SOFA trajectory, shorter time to clinical stabilization, and reduced ICU length of stay. A lower 28-day mortality was also observed, although this secondary finding requires cautious interpretation because of the modest sample size. These results support further multicenter evaluation of AI-integrated multi-omic decision support as a potential adjunct to conventional microbiological diagnostics and antimicrobial stewardship in early sepsis management.

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