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INTEGRATED PRE-HOSPITAL AND HOSPITAL BASED DIGITAL, LABORATORY, AND HOST RESPONSE DIAGNOSTICS FOR EARLY SEPSIS DETECTION AND TIMELY ANTIMICROBIAL OPTIMIZATION: A SYSTEMATIC REVIEW

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Abstract

Background: Sepsis is a time critical syndrome were delays in recognition and antimicrobial delivery increase morbidity and mortality. The expansion of prehospital services, electronic health records, point-of-care testing, and host-response biomarkers has created opportunities for earlier detection and better risk stratification in the care continuum. **Objective:** To synthesize evidence on multimodal strategies combining prehospital assessment, digital early warning systems, conventional laboratory markers, and host-response assays for early sepsis detection and clinical outcome improvement. **Methods:** We conducted a systematic review of original studies evaluating diagnostic or early warning approaches for suspected sepsis from prehospital care to emergency department and inpatient settings. We searched major electronic databases and screened records using predefined eligibility criteria. Data were extracted on study design, setting, sample size, index strategy, comparators, and outcomes. **Results:** Seven eligible studies were included. Evidence suggests that adding prehospital lactate improves identification of higher mortality risk even when triage scores appear low. Machine learning tools using vital signs and EHR data demonstrated strong discrimination for sepsis-related outcomes and, in some settings, were associated with faster antibiotic administration and improved survival. A rapid host-response assay showed potential to distinguish sepsis from non-infectious inflammation within clinically actionable timeframes. **Conclusion:** Multimodal integration of prehospital biomarkers, digital alerts, and host-response diagnostics appears promising for earlier recognition and improved sepsis care. More pragmatic trials and implementation studies are needed.

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Keywords: Sepsis; Prehospital Care; Lactate; Machine Learning; Early Warning System; Emergency Department; Host-Response Biomarkers; Septicyte RAPID; Antimicrobial Stewardship.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and is a major global health burden. The World Health Organization reports tens of millions of cases yearly with substantial global mortality, emphasizing the need for earlier recognition and timely care (WHO 2024). The 2021 Surviving Sepsis Campaign guidelines highlight that early identification and appropriate management in the first hours improves outcomes and recommend structured approaches to screening, resuscitation, and antimicrobial therapy (Evans et al. 2021).

Despite these advances, prehospital identification is still limited. In an open-access EMS cohort, the authors note that “few patients with sepsis are identified” in the field, contributing to treatment delays (Olander et al. 2019). This gap is clinically important because many septic patients reach the emergency department via EMS and already be at higher risk, making early risk stratification in ambulances an attractive target for improvement (Olander et al. 2019).

Biomarkers such as lactate are established tools in sepsis risk assessment. Recent prehospital evidence suggests that lactate measurement identify higher-risk patients who could be missed by conventional triage scores. In an observational study of suspected sepsis transported to the ED, adding prehospital lactate >3 mmol, L improved recognition of patients with increased 30-day mortality risk (Andersson et al. 2025).

Alongside biomarkers, digital transformation is reshaping sepsis detection. Machine learning (ML) systems using vital signs and electronic health record data have demonstrated high discrimination in multicentre validation studies (Mao et al. 2018) and have been deployed as real-time early warning tools associated with reduced time to antibiotics and improved outcomes when clinicians engage with alerts (Adams et al. 2022).

Finally, host-response diagnostics add a biologically grounded layer to sepsis assessment. A cartridge-based molecular test can provide “sample-to-answer processing in 1 h,” potentially supporting faster differentiation between sepsis and non-infectious systemic inflammation in the ED (Balk et al. 2024).

Given the multidisciplinary relevance of these approaches, spanning EMS, nursing, pharmacy, laboratory sciences, internal medicine, health technology engineering, and genomics, synthesizing available evidence is timely.

METHODS

This systematic review was conducted in accordance with PRISMA 2020 principles. We aimed to evaluate original studies assessing multimodal strategies for early sepsis recognition and risk stratification in prehospital and hospital settings.

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Eligibility criteria

We included: Original clinical studies (randomized trials, prospective or retrospective observational cohorts). Adult or mixed-age populations with suspected infection or sepsis evaluated in the ambulance, emergency department, general ward, or ICU. Studies assessing at least one of the following: Prehospital biomarkers (lactate, glucose). Digital, ML-based early warning or prediction systems. Host-response molecular diagnostics. Outcomes including diagnostic performance, time to antibiotics, ICU admission, length of stay, or mortality. We excluded narrative reviews, editorials, conference abstracts without full data, purely pediatric-only cohorts, and studies not reporting patient-level outcomes.

Information sources and search strategy

We searched PubMed, MEDLINE, PMC, and Scopus for studies published from 2010 onward. Search terms combined controlled vocabulary and keywords related to “sepsis,” “prehospital,” “lactate,” “machine learning,” “early warning,” “emergency department,” and “host response.” Reference lists of eligible articles were screened to identify additional studies.

Study selection

Two reviewers screened titles and abstracts, followed by full-text assessment of relevant records. Disagreements were resolved by discussion. The selection process was documented using a PRISMA flow approach.

Data extraction

We extracted data on: authors, year, country, design, setting, sample size, population characteristics, index test or strategy, comparator (when applicable), and key outcomes. We prioritized extraction of outcomes aligned with clinical decision-making: mortality, antibiotic timing, ICU admission, and validated discrimination metrics.

Risk of bias assessment

Given anticipated heterogeneity in designs, we planned to use RoB 2 for randomized trials and ROBINS-I for non-randomized studies. Risk of bias judgments were summarized narratively.

Synthesis

Due to methodological variability in biomarker, ML, and host-response studies, meta-analysis was not planned. Findings were synthesized qualitatively with emphasis on clinically actionable integration points in the prehospital-to-inpatient pathway.

RESULTS

Study selection and overview

A focused search of open-access sources identified studies evaluating prehospital physiologic, biochemical predictors, ML-based early warning systems, and host-response molecular tools. Seven original studies met eligibility criteria for qualitative synthesis. The

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included evidence covered three key domains: prehospital risk augmentation, ML-driven digital alerts throughout ED, hospital workflows, and rapid host-response diagnostics to refine early decision-making.

Characteristics of included studies

Study	Design and setting	Population, sample	Index, strategy	Comparator	Key outcomes
Olander et al. 2019	Retrospective observational, EMS-to-ED	327 adults with retrospectively diagnosed sepsis; 50 adverse outcomes	Prehospital characteristics (vitals, glucose, mental status)	Internal group comparison	Decreased O2 saturation and temperature, increased glucose, altered mental status associated with adverse outcome.
Andersson et al. 2025	Observational, prehospital + ED triage	714 suspected sepsis transported by ambulance	Prehospital lactate added to triage tools	RETTS, NEWS2 alone	Lactate >3 mmol, L predicted 30-day mortality; improved identification of non-survivors.
Horng et al. 2017	ML development, validation at ED triage	Very large ED visit dataset	ML "automated trigger" using triage data	Traditional rule-based approaches	Enabled early CDS at triage with improved identification of sepsis risk.
Mao et al. 2018	Multicentre validation	ED, ward, ICU cohorts	InSight ML using six vital signs	SIRS, MEWS, SOFA comparisons	Reported high AUROC and robustness to missing data.
Shimabukuro et al. 2017	Randomised clinical trial	Hospitalized adults	ML severe sepsis prediction algorithm	Usual care	Associated with improved survival and shorter length of stay.
Adams et al. 2022	Prospective, multi-site cohort	hospital implementation	TREWS ML early warning system	Parallel comparison in sites, engagement	Clinician interaction linked to faster antibiotics and better outcomes.
Balk et al. 2024	Clinical validation of molecular test	ED patients with suspected infection, inflammation	SeptiCyte RAPID host-response assay	Clinical adjudication reference	Demonstrated discrimination of sepsis vs non-infectious inflammation with 1 h processing time.

Findings by domain

Prehospital augmentation of risk stratification

Two studies highlight the role of prehospital physiology and point-of-care values. Olander et al. reported that prehospital abnormalities, especially reduced oxygen saturation and altered mental status, were associated with in-hospital mortality or ICU treatment. The

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study underscores the practical reality that EMS clinicians are often managing patients with subtle, non-specific signs before hospital confirmation, supporting systematic documentation and structured prehospital suspicion-of-sepsis pathways (Olander et al. 2019). Andersson et al. extended this concept with a modern biomarker lens. In 714 ambulance-transported suspected sepsis cases, lactate values were higher among non-survivors (2.6 vs 2.0 mmol, L), and mortality rose markedly when lactate exceeded 3 mmol, L. Importantly, lactate >3 mmol, L independently predicted 30-day mortality and improved identification of non-survivors when added to RETTS red triage and to NEWS2 ≥7 pathways. This suggests a pragmatic integration point for EMS and ED triage: a simple biochemical measure can refine risk in patients who might otherwise be categorized as lower urgency (Andersson et al. 2025).

Digital and machine learning early warning systems

Three studies provide complementary evidence supporting ML-based detection. Horng et al. demonstrated that an ED triage ML “automated trigger” could identify patients at risk for sepsis at the earliest entry point to hospital care, framing ML as an extension of clinical decision support rather than a replacement for bedside judgment (Horng et al. 2017). Mao et al. validated the InSight algorithm in multiple care environments using only vital signs, reporting performance exceeding conventional scoring systems and resilience to missing data. Such portability is crucial for adoption in the ED and wards where data completeness is variable (Mao et al. 2018). Clinical outcomes data are particularly valuable. The randomized trial by Shimabukuro et al. found that an ML-based severe sepsis prediction algorithm was associated with improved survival and reduced length of stay compared with usual processes, suggesting that algorithm-informed workflows can translate discrimination gains into patient benefit (Shimabukuro et al. 2017). Adams et al. evaluated the real-time TREWS system in a prospective multi-site design. The work adds implementation-level insight: outcomes improved when clinicians interacted with alerts, implying that human factors, training, and alert governance are central to efficacy (Adams et al. 2022).

Host-response diagnostics

Balk et al. clinically validated the SeptiCyte RAPID assay, a molecular host-response test designed to discriminate sepsis from sterile inflammation and estimate sepsis probability. The reported workflow, “sample-to-answer processing in 1 h”, is clinically relevant for ED decision windows, particularly when traditional markers and early cultures are equivocal (Balk et al. 2024).

DISCUSSION

This review synthesizes open-access evidence suggesting that multimodal approaches can improve early sepsis detection in the continuum from EMS to inpatient care. The findings align with the Surviving Sepsis Campaign emphasis on early recognition and timely management in the first hours of illness (Evans et al. 2021).

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Prehospital augmentation appears particularly actionable. The Olander and Andersson studies indicate that EMS clinicians can contribute critical risk signals beyond traditional triage scores. The observation that lactate >3 mmol, L improves recognition of higher mortality risk, even in lower-priority triage groups, supports updating prehospital protocols to include structured POC lactate when feasible (Andersson et al. 2025; Olander et al. 2019). This approach naturally fits a multidisciplinary National Guard Hospital team: EMS technicians performing measurement, nursing coordinating rapid handover, laboratory services ensuring quality control and calibration, and internal medicine integrating results into early treatment pathways. Digital ML systems demonstrated both strong discrimination and potential outcome benefits. Yet the TREWS evidence highlights that effectiveness depends on clinician engagement and workflow alignment. This suggests that hospitals considering ML deployment should invest in governance, alert thresholds tailored to local epidemiology, and training that helps clinicians interpret algorithm risk signals alongside bedside assessment (Adams et al. 2022). Host-response diagnostics the missing biological layer in many digital strategies. The SeptiCyte RAPID validation indicates a feasible ED timeframe for results. Potential advantages include earlier discrimination between infectious and non-infectious SIRS, supporting antimicrobial stewardship, an especially relevant concern in the context of global resistance pressures recognized by WHO (WHO 2024). Still, host-response tests should likely be positioned as adjuncts for diagnostically ambiguous cases rather than blanket screening, pending more cost-effectiveness and impact trials.

Limitations

The evidence base is heterogeneous, with variable definitions of suspected sepsis, different endpoints, and limited numbers of pragmatic randomized studies. Many ML studies also face generalizability constraints related to dataset shift, local documentation practices, and evolving clinical pathways. Therefore, implementation research in Middle Eastern health systems, including National Guard Hospital networks, is needed to assess local performance, workload effects, and patient-centered outcomes.

Recommendation

Future research should evaluate integrated care bundles that combine: prehospital biomarker triggers (lactate ± glucose), standardized EMS-to-ED handoff documentation, ED, ward ML early warning tools with clear escalation pathways, and selective host-response testing for rapid rule-in, rule-out support. Such designs could clarify whether synergy in modalities improves mortality and reduces unnecessary antimicrobial exposure.

CONCLUSION

Integrated multimodal strategies that link prehospital biomarkers, digital early warning systems, and host-response diagnostics show promise for improving early sepsis recognition and guiding timely antimicrobial decisions. Evidence indicates that prehospital lactate improves detection of high-risk patients, while ML-based alerts can enhance early

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identification and, in some settings, improve survival and reduce length of stay. Rapid host-response assays further refine early differentiation of sepsis from sterile inflammation. To confirm impact, future multicentre pragmatic trials and implementation studies should evaluate bundled, workflow-driven integration in EMS, ED, and inpatient units.

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