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# BIOMARKER-AUGMENTED SEPSIS RECOGNITION FROM SCENE TO ED: A SYSTEMATIC REVIEW OF PARAMEDIC, NURSING, AND LABORATORY INTEGRATION

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**Abstract**

**Background:** Early sepsis recognition in the prehospital/ED pathway is challenging. Beyond vital-sign–based scores, several host-response biomarkers (lactate, procalcitonin, presepsin, suPAR) improve triage and risk stratification. **Objective:** To synthesize evidence on biomarker-augmented sepsis recognition and risk stratification across the scene-to-ED continuum. **Methods:** Following PRISMA principles, we analyzed nine included original studies (prehospital/ED) and used 10 additional papers for discussion. Data items were population, setting, index biomarker/tool, comparators, and outcomes (diagnostic/prognostic accuracy, workflow effects, and patient outcomes). Risk of bias and applicability were narratively assessed. **Results:** Prehospital lactate consistently associated with short-term mortality and improved identification of higher-risk patients, particularly when ≥3 mmol/L, but effects on hard outcomes or bundle adherence were inconsistent. In ED cohorts, presepsin showed strong diagnostic/prognostic discrimination and suPAR improved risk stratification; however, large pragmatic trials found no mortality benefit from routine suPAR use alone. Combining biomarkers with parsimonious clinical scores (NEWS2/qSOFA) generally enhanced discrimination but heterogeneity limits firm recommendations. **Conclusions:** Biomarkers can sharpen early sepsis risk recognition, with the most reproducible prehospital signal for lactate. Yet, translation to improved patient-level outcomes remains uncertain. Future research should prioritize targeted biomarker-plus-score pathways, workflow integration (pre-alert/antibiotic readiness), and randomized evaluations of patient-centered outcomes.

**Keywords:** Sepsis; Prehospital; Emergency Department; Lactate; Presepsin; suPAR; Biomarkers; NEWS2; qSOFA; Risk Stratification.

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## INTRODUCTION

Sepsis continues to exact a high global burden, with mortality tightly linked to timely recognition and treatment from first medical contact through ED care. Vital-sign–based triage tools (NEWS2, qSOFA) are pragmatic but miss early deterioration and have modest discrimination in unselected EMS/ED populations. Systematic and narrative syntheses emphasize that no single biomarker has supplanted clinical assessment; however, several markers of host response and tissue hypoperfusion add prognostic and, at times, diagnostic value when paired with simple scores. Combinatorial approaches are therefore attractive in settings with compressed decision time and scarce resources [10,11].

In the prehospital domain, portable point-of-care (POC) lactate devices enable earlier risk assessment than waiting for laboratory results. A recent systematic review of non-trauma, prehospital patients found elevated lactate was generally associated with higher short-term mortality, with signals for influencing early treatment in suspected sepsis, but certainty of evidence was low due to heterogeneity and bias risks [12].

Within ED cohorts, presepsin (sCD14-ST) and suPAR have emerged as promising markers of dysregulated host response. Presepsin has shown high diagnostic AUCs for sepsis and prognostic value comparable to or better than procalcitonin in some studies [6,7]. suPAR levels reflect global immune activation and stratify risk across undifferentiated ED patients; nevertheless, a large cluster-randomized trial (TRIAGE III) demonstrated improved risk stratification without mortality reduction when suPAR was simply added to usual care, underscoring the difference between prognostic enrichment and actionable benefit [9,11].

Pairing biomarkers with concise scores balance feasibility and performance. A systematic review of ED sepsis studies concluded combinations of biomarkers with scoring systems often improve 28–30-day mortality prediction, though heterogeneity prevents endorsing a single combination; parsimonious scores (qSOFA/NEWS2) plus a routinely available marker were advocated for future testing [10].

Evidence suggests biomarkers, especially lactate prehospital and presepsin/suPAR in ED, can refine risk recognition. The pivotal question is not only accuracy but whether embedding these signals in protocolized pathways accelerates antibiotics and targeted resuscitation enough to improve outcomes.

## METHODS

Protocol & eligibility. We conducted a systematic review of nine original studies (prehospital/ED) and used ten additional peer-reviewed sources to inform the discussion. We included prospective or retrospective EMS/ED studies evaluating biomarker-augmented recognition or risk stratification for adult patients with suspected infection/sepsis, reporting diagnostic performance, workflow effects (time to lactate/antibiotics), or patient outcomes (mortality, ICU admission). We excluded pure

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ICU studies, pediatric cohorts, non-infectious indications, and studies without extractable sepsis-related outcomes.

Data items & extraction. We extracted: setting (prehospital vs. ED), design, population size, index biomarker(s) and comparator (clinical score or usual care), thresholds, outcomes (AUC/AUROC, OR/HR, sensitivities/specificities), and process metrics (door-to-antibiotic, bundle adherence). Where reported, we recorded adjusted effect sizes. Primary outcomes were diagnostic/prognostic accuracy and short-term mortality; secondary outcomes included time metrics and ICU use.

Risk of bias & applicability. Given heterogeneous designs, we used domain-based appraisal (selection, index test, reference standard, flow/timing; confounding for prognostic studies). Prehospital lactate studies commonly faced selection and confounding risks; ED biomarker studies often risked spectrum/verification biases. Pragmatic trials (suPAR implementation) had lower selection bias but intervention fidelity concerns.

Synthesis. Due to clinical and methodological heterogeneity (settings, biomarkers, thresholds, outcomes), we performed narrative synthesis. We grouped findings by (1) prehospital biomarkers (primarily lactate), (2) ED biomarkers (presepsin, suPAR), and (3) combinations with early-warning scores. We constructed two summary tables (study characteristics; key outcomes/effects). No meta-analysis was attempted.

## RESULTS

### Study overview

Nine included studies spanned prehospital (lactate-focused) and ED cohorts (presepsin/suPAR, POC lactate). Table 1 summarizes characteristics; Table 2 lists key outcomes.

### Prehospital lactate

A large, prospective EMS cohort of suspected sepsis found higher prehospital lactate in non-survivors; lactate >3 mmol/L independently predicted 30-day mortality (OR =2.2), and added lactate improved identification of non-survivors within high-priority triage strata and among patients not otherwise flagged high-risk [2]. Another multi-centre Swedish EMS study in a general adult population showed POC lactate incrementally improved prediction over RETTS triage and a richer “base” model, but absolute gains were small and lactate alone performed at chance-level, supporting selective rather than universal use [3]. A retrospective county-wide study comparing 11 prehospital screening tools reported that adding lactate/CRP/WBC to NEWS increased specificity (>80%) but reduced sensitivity for sepsis identification, underscoring trade-offs when biomarkers are layered onto triage tools [4].

A recent systematic review of prehospital lactate in non-trauma patients (15 cohorts) corroborated that elevated lactate generally tracks worse short-term outcomes, with

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limited, low-certainty evidence that access to prehospital lactate changes early treatment, particularly in suspected sepsis [12].

### ED lactate POCT and workflow

A pre–post ED study introducing lactate POCT shortened time-to-result (=53→33 min) and slightly increased repeat lactate measurement but did not improve composite bundle adherence or 30-day mortality overall, suggesting that faster numbers alone do not guarantee pathway execution [5].

### Presepsin in the ED

A multicenter Italian ED study found presepsin levels higher in sepsis vs. SIRS, with added *prognostic* value, higher baseline presepsin predicted 60-day mortality; PCT showed higher diagnostic AUC, while presepsin better tracked outcome risk [6]. More recent ED work reported very high diagnostic accuracy for presepsin (AUC =0.95) comparable to PCT, and that combining presepsin/PCT with an early-warning score achieved the highest diagnostic performance, aligning with the “biomarker + parsimonious score” hypothesis [7].

### suPAR in the ED

A cluster-randomized implementation trial (TRIAGE III; n=16,800) showed that routine suPAR measurement improved risk stratification (disposition/LOS/readmission signals) but did not reduce 30-day or 10-month mortality, emphasizing that prognostic enrichment requires embedded action pathways to influence outcomes [9]. Complementarily, a randomized trial targeting patients with qSOFA=1 and suPAR≥12 ng/mL (SUPERIOR) found that suPAR-guided early meropenem reduced early deterioration (ΔSOFA≥1 at 24h) vs. placebo; the trial was prematurely stopped (pandemic-related), limiting precision and generalizability [8]. Narrative/physiology reviews reinforce suPAR’s role as a non-specific prognostic marker reflecting immune activation: useful to “rule-in” acuity rather than diagnose infection per se [11].

### Combinations with clinical scores.

A systematic review of combinations reported improved 28–30-day mortality prediction when biomarkers (lactate, IL-6, PCT) were paired with simplified scores (SAPS-2, qSOFA), but heterogeneity precluded endorsing a definitive pairing and highlighted the appeal of readily available markers and parsimonious scores for ED practicality [10].

### Workflow integration and time-to-treatment.

Evidence outside biomarker trials shows that EMS ALS transport and structured ED sepsis alerts can shorten door-to-antibiotics and key bundle elements, although effects vary and not extend to mortality without comprehensive process redesign [13,15,16]. Moreover, mandated bundle analyses associate faster antibiotics with lower mortality, underscoring why biomarker-triggered pathways should focus on treatment timeliness and reliability [45].

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## Table 1: Characteristics of included studies

| Study | Setting & design | Population | Index biomarker / tool | Comparator | Primary outcomes |
|---|---|---|---|---|---|
| Brant 2020 [1] | Prehospital, prospective cohort | Non-trauma EMS adults at risk for sepsis (n=452) | IL-6, IL-10, CRP, PCT, troponin, lactate panel | Clinical risk score alone | AUROC for “community sepsis” within 48h; reclassification |
| Andersson 2025 [2] | Prehospital, prospective | Suspected sepsis (n=714) | Lactate (continuous & cutpoints) | RETTS/NEWS2 | 30-day mortality; ED sepsis; IH mortality; multivariable ORs |
| Magnusson 2024 [3] | Prehospital, multicentre prospective | General EMS adults (n=4,546) | POC lactate | RETTS/base models | Time-sensitive dx, SOFA≥2, 30-day mortality; added value |
| Olander 2024 [4] | Prehospital, retrospective | Suspected infection EMS (n=3,225) | WBC/CRP/lactate + 11 tools | NEWS/RETTS etc. | Sensitivity/specificity for sepsis; non-conveyance suitability |
| Lee 2024 [5] | ED pre–post | qSOFA-positive ED sepsis (n=1,191) | Lactate POCT | Central lab pathway | Bundle adherence; 30-day mortality; time-to-result |
| Ulla 2013 [6] | ED prospective | SIRS±suspected sepsis (n=189) | Presepsin | Procalcitonin | Diagnostic AUC; 60-day mortality prognostics |
| Piccioni 2025 [7] | ED prospective | Suspected sepsis | Presepsin | PCT; EWS | Diagnostic AUC; combined model performance |
| Adami 2024 [8] | ED RCT (SUPERIOR) | qSOFA=1, suPAR≥12 ng/mL | suPAR-guided meropenem vs placebo | , | Early deterioration (ΔSOFA≥1 at 24h) |
| Schultz 2018 [9] | ED cluster RCT (TRIAGE III) | Unselected ED admissions (n=16,801) | suPAR implementation | Usual care | 30-day/10-month mortality; risk stratification metrics |

## Table 2: Key findings and effect estimates

| Domain | Summary of effects |
|---|---|
| **Prehospital lactate** | Higher lactate predicted mortality; ≥3 mmol/L associated with increased 30-day mortality (adjusted OR ~2.2) and improved identification of non-survivors in lower-priority triage groups; incremental value over RETTS/NEWS2 modest in unselected EMS cohorts [2–4, 12]. |
| **ED lactate POCT** | Reduced time-to-lactate but did not improve overall SSC bundle adherence or 30-day mortality in a single-center pre–post design [5]. |
| **Presepsin** | Diagnostic AUC high (=0.95), comparable to PCT; initial presepsin associated with mortality; best performance when combined with an EWS [6, 7]. |
| **suPAR** | Improves ED risk stratification; implementation alone did not reduce mortality (TRIAGE III). Targeted suPAR-guided early antibiotics in qSOFA=1 reduced early deterioration in a small RCT [8, 9, 11]. |
| **Scores + biomarkers** | Combinations generally outperform single elements for 28–30-day mortality prediction, but heterogeneity and feasibility considerations favor simple scores plus a widely available biomarker [10]. |
| **Workflow/time effects** | ALS transport and ED sepsis alert/protocols can shorten door-to-antibiotics/fluids; mandated program analysis links hourly antibiotic delays to higher mortality, relevant for embedding biomarker triggers into rapid treatment pathways [13, 15, 16, 45]. |

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## DISCUSSION

This review integrates prehospital and ED evidence to address a practical question: can biomarkers improve early sepsis recognition and change outcomes? Three themes emerge. First, lactate remains the most actionable prehospital biomarker. It robustly tracks short-term mortality in suspected sepsis and up-triage otherwise “non-red” patients, mainly triggering earlier ED mobilization [2,12]. In unselected EMS populations the incremental predictive gain is modest, arguing for selective use (suspected infection, ambiguous risk) rather than blanket testing [3,4,12]. Presepsin shows strong diagnostic/prognostic performance and, importantly, pairs well with simple early-warning scores [6,7,10]. suPAR is an excellent prognostic “thermometer” of systemic inflammation; however, routine measurement without an action protocol did not improve mortality (TRIAGE III). Conversely, a small randomized trial suggested that *targeted* suPAR-guided, early broad-spectrum therapy among qSOFA=1 patients can reduce early deterioration [8,9,11]. Together, these findings support *targeted enrichment* strategies rather than universal biomarker deployment. Evidence external to biomarker trials underscores that EMS ALS care and ED alert-protocols can shorten door-to-antibiotics, and that each hour of antibiotic delay is associated with higher mortality under statewide mandates [13,15,45]. Yet a pre–post lactate POCT study showed shorter turnaround without better bundle adherence or mortality, an important caution: numbers alone don’t save lives; *reliably acting on them does* [5,16]. For prehospital systems, consider selective lactate testing (suspected infection with equivocal NEWS2/RETTS) embedded in a sepsis pre-alert that primes ED antibiotics/fluids. In the ED, leverage presepsin (and/or PCT) with a parsimonious score to triage and re-prioritize diagnostics while testing suPAR-enriched early-antibiotic pathways in intermediate-risk patients. Health-system redesign (nurse-driven protocols, antibiotic readiness, lactate-guided resuscitation) should be co-implemented and prospectively evaluated.

**Limitations.** Our synthesis was confined to a predefined corpus; heterogeneity precluded meta-analysis. Several prehospital studies faced confounding and selection bias; the suPAR RCT was underpowered. Feasibility, costs, and antimicrobial stewardship must be balanced against potential benefits.

## CONCLUSION

In the scene-to-ED pathway, biomarkers, most reproducibly, lactate prehospital and presepsin/suPAR in the ED, enhance early sepsis risk recognition beyond vital signs alone. However, improved discrimination has not consistently translated into better outcomes unless biomarker signals trigger faster, protocolized treatment. The optimal near-term strategy is *targeted enrichment*: pair parsimonious scores with a small set of actionable biomarkers, embed them in prehospital alerts and ED pathways, and evaluate effects on antibiotic timeliness and mortality in pragmatic trials. Precision triage must be coupled to reliable execution to improve sepsis outcomes.

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