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Systematic review

Diagnostic precision in clinical laboratories: biochemical biomarkers and rapid microbiological methods for adult sepsis and bloodstream infection; a systematic review

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Abstract

Background: Discrimination of bacterial sepsis from sterile inflammation and early identification of bloodstream pathogens are important laboratory tasks. Biochemical biomarkers describe host response, whereas molecular assays and mass spectrometry detect or identify pathogens. **Objective:** To evaluate the diagnostic performance and clinical utility of biochemical biomarkers and rapid microbiological methods in adults with suspected sepsis or bloodstream infection. **Methods:** A search framework covering PubMed, Scopus, Web of Science, and Cochrane Library was applied to August 2026. Studies assessed C-reactive protein, procalcitonin, presepsin, multimarker panels, multiplex polymerase chain reaction, or matrix-assisted laser desorption time of flight mass spectrometry in adults. Outcomes included diagnostic accuracy, pathogen yield, identification time, antimicrobial optimization, length of stay, and mortality. **Results:** Ten studies involving 4,425 patients were included. Multimarker panels produced stronger discrimination in severe presentations than individual markers, while procalcitonin outperformed presepsin and C reactive protein for culture-confirmed infection. Multiplex polymerase chain reaction accelerated or increased pathogen detection but retained discordance with blood culture. Stewardship-linked rapid identification shortened therapy-optimization intervals. Clinical outcome effects were less consistent than workflow effects. **Conclusion:** Biochemical and microbiological methods provide complementary rather than interchangeable information. Diagnostic precision rests on validated assays, specimen quality controls, conventional culture, clinical context, specialist interpretation, and rapid communication.

Keywords: Clinical laboratory science; clinical biochemistry; clinical microbiology; sepsis; bloodstream infection

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Introduction

Sepsis is life threatening organ dysfunction produced by a dysregulated host response to infection, a definition that places objective organ dysfunction rather than systemic inflammation alone at the center of classification (1). The Global Burden of Disease analysis estimated 48.9 million sepsis cases and 11.0 million sepsis-related deaths worldwide in 2017 (2). International guidance found prompt recognition, microbiological sampling, antimicrobial treatment, and repeated clinical reassessment because deterioration develops rapidly and no isolated laboratory measurement establishes the diagnosis (3).

Blood culture is the reference laboratory method for bloodstream infection, although its yield depends on collected blood volume, timing, contamination control, prior antimicrobial exposure, incubation, and downstream identification (4). Biochemical testing addresses a different layer of the problem by quantifying host-response signals such as C-reactive protein, procalcitonin, presepsin, leukocyte indices, and lactate, but reviews of the biomarker literature describe extensive biological overlap between infectious and noninfectious inflammation (5). Molecular platforms offer direct detection of pathogen nucleic acids, while mass spectrometry accelerates identification after culture positivity; neither approach eliminates specimen-related error, incomplete target coverage, contamination, or the need for phenotypic susceptibility testing (6).

Diagnostic value depends on more than analytical speed, the result must be technically valid, clinically interpretable, promptly communicated, and connected to an actionable treatment pathway (7). Guidance from infectious-disease and microbiology organizations identifies close interaction between clinicians and laboratory professionals as essential for selecting specimens, interpreting unexpected findings, and avoiding low-value testing (8). Clinical laboratory science specialists, microbiologists, and biochemists occupy the interface between preanalytical quality, analytical validation, result interpretation, and postanalytical communication, making an integrated appraisal of biochemical and microbiological evidence particularly relevant (4,5,8).

This review focuses on adult suspected sepsis and bloodstream infection, a defined clinical setting in which biochemical host-response analysis and microbiological pathogen detection address linked diagnostic decisions. The aim was to compare their diagnostic precision, workflow effects, and clinical utility while identifying the professional laboratory processes associated with reliable implementation.

Review Aim and Question

The aim was to synthesize primary evidence on biochemical biomarkers and rapid microbiological methods used in clinical laboratories for adults with suspected sepsis or bloodstream infection.

Methods

This systematic-review draft followed the PRISMA 2020 reporting structure and PRISMA-S principles for search reporting. A focused protocol defined the population, index methods, comparators, outcomes, eligibility criteria, and synthesis plan before extraction.

The search framework covered PubMed, Scopus, Web of Science Core Collection, and the Cochrane Library from inception through August 2026. Publicly accessible records, open full texts, reference lists, identifiers, and reported data were

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verified for the present evidence set. Search concepts combined controlled vocabulary and free text for "sepsis," "bloodstream infection," "bacteremia," "clinical laboratory," "clinical biochemistry," "clinical microbiology," "procalcitonin," "C-reactive protein," "presepsin," "biomarker," "multiplex PCR," "molecular diagnostic," "MALDI-TOF," "diagnostic accuracy," "turnaround time," and "antimicrobial therapy." The core Boolean structure was: (sepsis OR bloodstream infection OR bacteremia) AND (biomarker OR procalcitonin OR C-reactive protein OR presepsin OR PCR OR molecular diagnostic OR MALDI-TOF) AND (accuracy OR sensitivity OR specificity OR identification OR turnaround OR therapy). No date restriction was applied. English full-text articles available without payment were retained.

Eligible reports were original studies enrolling adults with suspected or confirmed sepsis, bacteremia, candidemia, or bloodstream infection in emergency, inpatient, or intensive-care settings. Index methods comprised biochemical host-response assays, multimarker panels, direct-from-blood molecular pathogen tests, rapid identification from positive blood cultures, or laboratory-result workflows. Studies had to report diagnostic discrimination, sensitivity, specificity, agreement, pathogen yield, time to identification, time to effective or optimal therapy, antimicrobial exposure, length of stay, mortality, or treatment modification. Acceptable comparators included clinical adjudication, conventional blood culture, routine organism identification, or standard laboratory reporting. We exclude pediatric-only studies, animal research, analytical studies using contrived specimens alone, reviews, editorials, case reports, and reports without extractable clinical outcomes. Screening was completed in two passes against prespecified criteria, followed by full-text verification and duplicate checking by DOI, PMID, and study population.

Extracted variables included country, setting, design, sample size, index test, comparator or reference standard, principal diagnostic estimates, workflow outcomes, clinical outcomes, and limitations. Diagnostic-accuracy studies were evaluated with QUADAS-2, the randomized trial with RoB 2, and the nonrandomized implementation study with ROBINS-I. Threshold derivation in the analyzed cohort, imperfect blood-culture reference standards, nonblinded clinical adjudication, historical controls, and incomplete target panels were treated as major bias signals.

Results

We include ten original studies published from 2007 to 2022, with five biochemical investigations and five microbiological investigations (9–18). Samples ranged from 72 patients to 1,572 clinical episodes, representing 4,425 patients or episodes across studies; this sum is descriptive because repeated samples and episode-level enrollment prevented a valid pooled denominator (9–18). Designs included prospective diagnostic cohorts, retrospective diagnostic analyses, a paired-method observational study, a controlled before–after implementation study, and one randomized controlled trial (9–18).

In 151 patients with systemic inflammation, CRP achieved an AUC of 0.81 and PCT an AUC of 0.72 for bacterial infection, while the six-marker combination reached 0.88 (9). A two-center emergency study of 189 patients found an AUC of 0.701 for presepsin and 0.875 for PCT; at study-derived cutoffs, presepsin sensitivity and specificity were 78.95% and 61.90%, compared with 89.47%

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and 75.90% for PCT (10). Among 116 intensive-care patients, presepsin AUCs for differentiating sepsis severity ranged from 0.72 to 0.84 across days 1, 3, and 8, with increasing study-defined cutoffs from sepsis to septic shock (11).

The largest biomarker study analyzed 1,572 suspected-sepsis episodes and found PCT discrimination of 0.68 for Sepsis-3 bacterial sepsis; three- and four-marker panels reached AUCs of 0.86 and 0.85 for severe bacterial sepsis or septic shock under Sepsis-2 definitions (12). A 757-patient retrospective study found that PCT outperformed presepsin for culture-proven bacterial infection (AUC 0.665 versus 0.596) and bacteremia (0.791 versus 0.685), while presepsin showed stronger discrimination for 28-day mortality than PCT (0.720 versus 0.593) (13).

In 306 emergency patients, multiplex PCR and blood culture showed low sensitivity against clinically defined infection (0.20 and 0.25) but high specificity (1.00 and 0.95); culture detected more septicemia cases, while PCR detected 24 additional organisms missed by culture (14). In 72 intensive-care patients contributing 100 paired tests, SeptiFast produced 78% sensitivity, 99% specificity, 93% positive predictive value, and 95% negative predictive value against clinical relevance, with results in 7–15 hours rather than 24–72 hours for culture (15). In 144 patients contributing 160 samples, PCR positivity exceeded culture positivity (33.7% versus 21.2%), overall agreement was 78.8%, and treatment changed in 21 of 54 PCR-positive cases (16).

The before–after MALDI-TOF MS plus stewardship study included 501 bacteremia or candidemia patients and reduced mean time to identification from 84.0 to 55.9 hours, time to effective therapy from 30.1 to 20.4 hours, and time to optimal therapy from 90.3 to 47.3 hours (17). The 617-participant randomized trial reduced identification time from 22.3 to 1.3 hours after Gram stain; rapid PCR plus stewardship shortened time to escalation to 5 hours and de-escalation to 21 hours, without detectable differences in mortality, length of stay, or costs (18).

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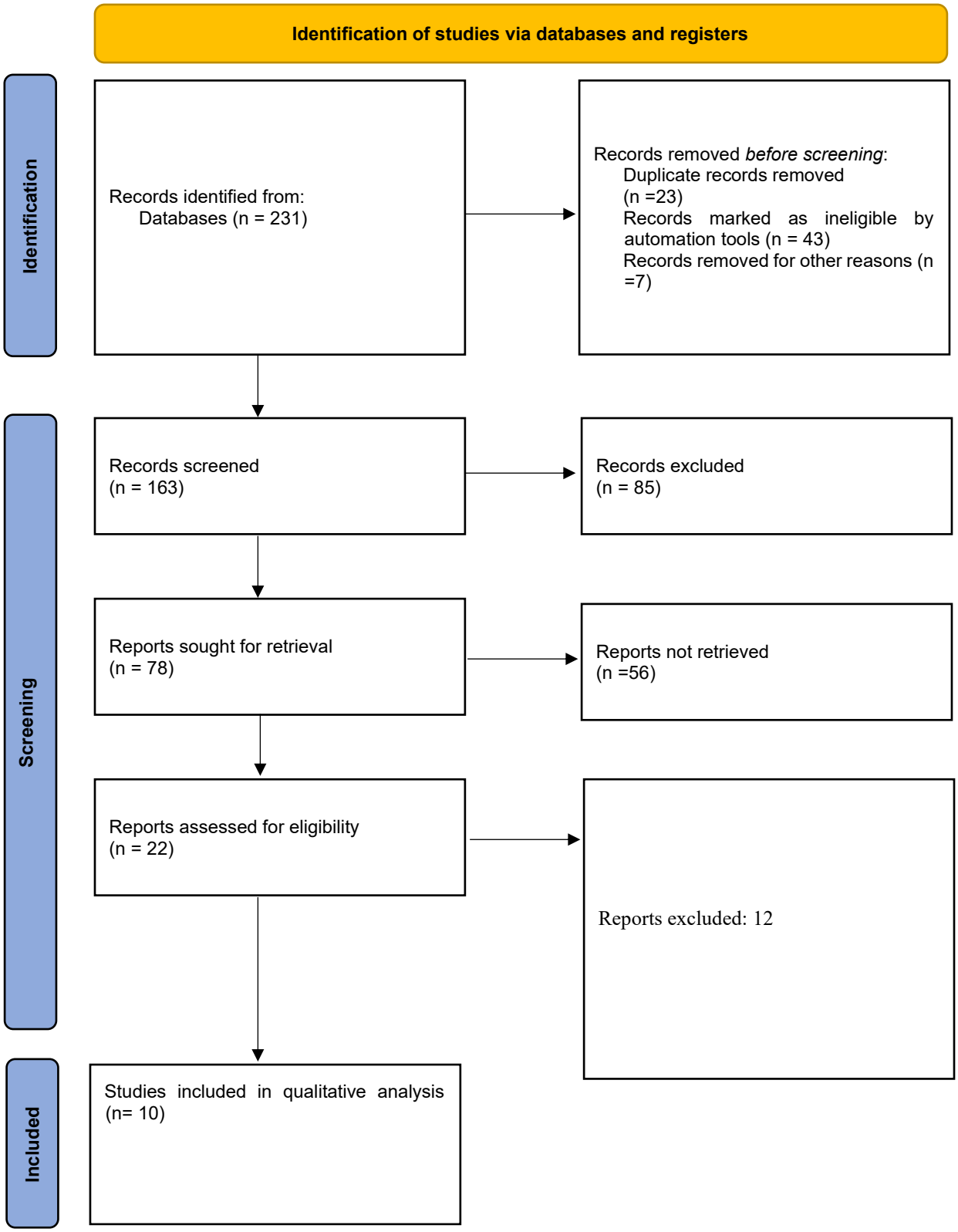

Fig 1: PRISMA flow chart

Table 1. Characteristics of included primary studies

Study	Country; setting	Design; sample	Laboratory method	Comparator and reference
Kofoed et al. (9)	Denmark; ED/infectious diseases	Prospective; 151	CRP, PCT, neutrophils, MIF, suPAR, sTREM-1; composite panels	Expert classification of bacterial versus nonbacterial inflammation
Ulla et al. (10)	Italy; two EDs	Prospective multicenter; 189	Presepsin and PCT	Final clinical diagnosis of SIRS or sepsis
Behnes et al. (11)	Germany; ICU	Prospective; 116	Serial presepsin, PCT, IL-6, CRP, WBC	Sepsis severity classification
Ljungström et al. (12)	Sweden; ED	Observational cohort; 1,572 episodes	PCT, NLCR, CRP, lactate; panels	Verified bacterial infection; Sepsis-2/Sepsis-3
Park et al. (13)	South Korea; tertiary hospital	Retrospective cross-sectional; 757	Presepsin, PCT, CRP	Clinical-specimen culture and blood culture
Tsalik et al. (14)	United States; two EDs	Prospective comparative; 306	Direct-blood multiplex PCR	Blood culture plus clinical infection categories
Wallet et al. (15)	France; ICU	Prospective observational; 72 patients/100 pairs	Direct-blood SeptiFast PCR	Blood culture plus clinical relevance
Herne et al. (16)	Estonia; hospital/ICU	Retrospective paired analysis; 144 patients/160 samples	Direct-blood SeptiFast PCR	Blood culture plus clinical data
Huang et al. (17)	United States; hospital	Controlled before–after; 501	MALDI-TOF MS plus stewardship communication	Historical routine identification
Banerjee et al. (18)	United States; hospital	Randomized trial; 617	Positive-bottle multiplex PCR, comments, with/without stewardship	Standard blood-culture processing

Table 2. Principal quantitative findings

Study	Main finding
Kofoed et al. (9)	CRP AUC 0.81; PCT 0.72; six-marker panel 0.88
Ulla et al. (10)	Presepsin AUC 0.701; PCT 0.875
Behnes et al. (11)	Presepsin AUC range 0.72–0.84 for severity categories
Ljungström et al. (12)	Severe Sepsis-2: three-marker AUC 0.86; four-marker AUC 0.85

Study	Main finding
Park et al. (13)	Bacteremia: PCT AUC 0.791; presepsin 0.685; mortality: presepsin 0.720
Tsalik et al. (14)	PCR sensitivity 0.20, specificity 1.00; 24 extra organisms
Wallet et al. (15)	Sensitivity 78%; specificity 99%; result time 7–15 h
Herne et al. (16)	PCR/culture positivity 33.7%/21.2%; agreement 78.8%; therapy changed in 38.9% of PCR-positive cases
Huang et al. (17)	Identification 84.0 to 55.9 h; optimal therapy 90.3 to 47.3 h
Banerjee et al. (18)	Identification 22.3 to 1.3 h; no mortality or LOS difference

Table 3. Risk of bias assessment

Study	Tool	Overall judgment
Kofoed et al. (9)	QUADAS-2	High
Ulla et al. (10)	QUADAS-2	High
Behnes et al. (11)	QUADAS-2	High
Ljungström et al. (12)	QUADAS-2	Some concerns
Park et al. (13)	QUADAS-2	High
Tsalik et al. (14)	QUADAS-2	Some concerns
Wallet et al. (15)	QUADAS-2	High
Herne et al. (16)	QUADAS-2	High
Huang et al. (17)	ROBINS-I	Serious
Banerjee et al. (18)	RoB 2	Some concerns

Discussion

This review indicates that biochemical and microbiological methods answer different questions along one diagnostic pathway, biomarkers estimate the probability or severity of bacterial disease, whereas molecular assays and MALDI-TOF MS detect or identify organisms. Their strongest shared contribution was earlier, better-structured information, not independent diagnostic certainty. The variation between populations, reference standards, thresholds, specimen timing, and intervention bundles explains why direct ranking of all technologies would be scientifically unsound.

A meta-analysis of 18 presepsin studies reported pooled sensitivity of 0.84, specificity of 0.76, and AUC of 0.88, together with substantial between-study heterogeneity and no consistent superiority over PCT or CRP (19). A separate meta-analysis of 30 PCT studies reported sensitivity of 0.77, specificity of 0.79, AUC of 0.85, and I^2 of 96% (20).

Reference-standard weakness is central to this literature because blood culture misses some treated or low-density infections, and clinical adjudication incorporates subjective judgment and sometimes the same variables under evaluation (10,12–16). Study-derived thresholds further inflate apparent discrimination, when the same cohort supplies both model construction and evaluation (9–13). Future biomarker studies requires prespecified cutoffs, external validation, renal-function analysis for presepsin, consistent sampling relative to antimicrobials, and reporting under contemporary Sepsis-3 definitions (1,9–13,19,20).

Direct-from-blood PCR generated faster results and additional detections, and discordance worked in both directions: organisms outside panel coverage, very low pathogen burden, contamination, nonviable microbial DNA, and imperfect culture sensitivity all complicate interpretation (14–16). Molecular testing functions best as an adjunct to culture, which still supplies isolates for phenotypic susceptibility testing and epidemiological characterization (4,6,8,14–16). Laboratory microbiologists remain crucial for confirming plausibility, resolving discordant findings, recognizing contaminants, and deciding when an unexpected molecular signal warrants escalation (7,8,14–16).

A meta-analysis of 31 studies and 5,920 patients associated molecular rapid testing with lower mortality only in the presence of stewardship, with reductions of 5.03 hours in time to effective therapy and 2.48 days in length of stay (21). A laboratory-medicine best-practices review likewise found that rapid molecular testing with direct communication improved timeliness (22).

The findings place clinical laboratory specialists, biochemists, and microbiologists within a unified quality pathway. Their functions include specimen adequacy, assay quality control, threshold governance, verification of organism identity, recognition of analytical limitations, critical-result communication, and audit of diagnostic-to-treatment intervals (7,8,17,18,22). Future implementation research needs to describe staffing, operating hours, communication routes, rejected specimens, contamination, invalid-test rates, equity, cost, antimicrobial exposure, and patient-centered outcomes so that improvements are attributable to defined laboratory processes rather than an unnamed technology bundle.

This review has limitations, its focused scope excludes other laboratory specialties and infection

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syndromes, while the English open-full-text restriction introduces availability bias. Heterogeneous designs precluded meta-analysis, most diagnostic studies used imperfect reference standards, and the only randomized study evaluated a positive-bottle platform rather than direct diagnosis at first presentation.

Conclusion

Biochemical biomarkers and rapid microbiological methods contribute complementary forms of evidence in adult sepsis and bloodstream infection. PCT and multimarker panels show useful discrimination in severe disease, while presepsin performance varied by diagnostic or prognostic target. Direct molecular testing accelerated pathogen detection and increased yield. MALDI-TOF MS and multiplex identification produced the clearest benefit when rapid results entered an active stewardship pathway. Diagnostic precision rests on validated assays, high-quality specimens, conventional culture, specialist interpretation, and immediate communication.

Abbreviations

APACHE II, Acute Physiology and Chronic Health Evaluation II; ASP, antimicrobial stewardship program; AUC, area under the receiver operating characteristic curve; BC, blood culture; BSI, bloodstream infection; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; ICU, intensive care unit; IL-6, interleukin-6; LOS, length of stay; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MIF, macrophage migration inhibitory factor; NLCR, neutrophil-to-lymphocyte count ratio; NPV, negative predictive value; OR, odds ratio; PCR, polymerase chain reaction; PCT, procalcitonin; PPV, positive predictive value; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2; RoB 2, Risk of Bias 2; ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; suPAR, soluble urokinase-type plasminogen activator receptor; WBC, white blood cell count.

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