SYSTEMATIC REVIEW

OPEN

The Diagnostic Utility of Host RNA Biosignatures in Adult Patients With Sepsis: A Systematic Review and Meta-Analysis

Mervin V. Loi, MBBS, MSc, FRCPCH[1]

Rehena Sultana, MSc, MBA[2]

Tuong Minh Nguyen, MSc[3]

Shi Ting Tia, [4]

Jan Hau Lee, MBBS, MCI, MRCPCH[1,5]

Daniel O'Connor, DPhil[6,7]

OBJECTIVES: Sepsis is a life-threatening medical emergency, with a profound healthcare burden globally. Its pathophysiology is complex, heterogeneous and temporally dynamic, making diagnosis challenging. Medical management is predicated on early diagnosis and timely intervention. Transcriptomics is one of the novel "-omics" technologies being evaluated for recognition of sepsis. Our objective was to evaluate the performance of host gene expression biosignatures for the diagnosis of all-cause sepsis in adults.

DATA SOURCES: PubMed/Ovid Medline, Ovid Embase, and Cochrane databases from inception to June 2023.

STUDY SELECTION: We included studies evaluating the performance of host gene expression biosignatures in adults who were diagnosed with sepsis using existing clinical definitions. Controls where applicable were patients without clinical sepsis.

DATA EXTRACTION: Data including population demographics, sample size, study design, tissue specimen, type of transcriptome, health status of comparator group, and performance of transcriptomic biomarkers were independently extracted by at least two reviewers.

DATA SYNTHESIS: Meta-analysis to describe the performance of host gene expression biosignatures for the diagnosis of sepsis in adult patients was performed using the random-effects model. Risk of bias was assessed according to the Quality Assessment of Diagnostic Accuracy Studies-2 tool. A total of 117 studies ($n = 17{,}469$), comprising 132 separate patient datasets, were included in our final analysis. Performance of transcriptomics for the diagnosis of sepsis against pooled controls showed area under the receiver operating characteristic curve (AUC, 0.86; 95% CI, 0.84–0.88). Studies using healthy controls showed AUC 0.87 (95% CI, 0.84–0.89), while studies using controls with systemic inflammatory response syndrome (SIRS) had AUC 0.84 (95% CI, 0.78–0.90). Transcripts with excellent discrimination against SIRS controls include UrSepsisModel, a 210 differentially expressed genes biosignature, microRNA-143, and Septicyte laboratory.

CONCLUSIONS: Transcriptomics is a promising approach for the accurate diagnosis of sepsis in adults and demonstrates good discriminatory ability against both healthy and SIRS control subjects.

KEYWORDS: biomarkers; diagnosis; gene expression; sepsis; transcriptomics

Sepsis is a life-threatening clinical syndrome encompassing heterogeneous disease expression and is marked by a pathologically unbalanced host response to severe infection resulting in tissue injury (1). The healthcare burden attributable to sepsis is substantial (2), with an estimated 5.3 million deaths globally per annum (3). Progress in understanding the pathophysiological processes underpinning sepsis has unfortunately not been matched by

Copyright © 2025 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.0000000000001212

KEY POINTS

Question: What is the accuracy of gene expression biomarkers for the diagnosis of clinical sepsis in adult patients?

Findings: Transcriptomic biomarkers showed good discriminatory ability for the diagnosis of sepsis against pooled controls and had superior performance compared with C-reactive protein and procalcitonin. This good discriminatory ability was maintained in subgroup analyses, where control patients had systemic inflammatory response syndrome.

Meaning: Transcriptomics may improve the diagnosis of sepsis in adults, compared with existing biomarkers in clinical use. Further studies aimed at validating the most promising biosignatures are needed to support its introduction into clinical practice.

a proportionate increase in our armamentarium of treatment options (4–8).

The mainstay of management remains the timely use of appropriate antimicrobials and source control, along with organ support (9, 10). Sepsis treatment should commence with minimal delay (11), with early recognition and intervention being associated with improved outcomes (12–14). The ability to rapidly identify and accurately differentiate sepsis from other pathological states is, however, hampered by inadequate biomarker performance (15).

High-throughput technologies have enabled rapid progress in the field of transcriptomics, which is the study of host RNA expression. This research has expanded beyond messenger RNA (mRNA) to include evaluation of noncoding RNAs (ncRNA) (16). Transcriptomics can provide a granular profile of host response to disease and has already demonstrated utility for differentiating bacterial from nonbacterial causes in patients with acute febrile illness (17). This systematic review and meta-analysis aimed to evaluate the performance of host RNA transcriptomic biosignatures for the identification of patients with sepsis to assess its utility in sepsis diagnosis and management.

METHODS

Study Design and Data

We conducted a systematic review and meta-analysis of studies investigating gene expression for sepsis diagnosis in human subjects. Our prespecified protocol was prospectively registered with the PROSPERO (CRD42023397271). We reported findings according to the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (2021) (18).

Search Strategy and Eligibility Criteria

We systematically searched PubMed/Ovid Medline, Ovid Embase, and Cochrane databases from inception to June 2023 (final search date: June 22, 2023) for eligible studies. Studies that evaluated the performance of human host gene expression biosignatures for the diagnosis of sepsis in humans were eligible for inclusion. Studies performed in all clinical areas were included. There was no restriction on pathogen type or immunological status. Secondary studies reanalyzing transcriptomic data held in public databases, such as the National Centre for Biotechnology Information (Gene Expression Omnibus) and the European Bioinformatics Institute (ArrayExpress) were included. All reasonable effort was made to ensure clinical datasets that were published in more than one article were not duplicated. Key references and review articles were hand-searched for further relevant studies for inclusion.

Our systematic review initially included all studies evaluating the use of transcriptomics for the diagnosis and prognosis of sepsis in adults, children, and neonates (for full Medline search strategy, see **Fig. S1**, http://links.lww.com/CCX/B464), but this was subsequently narrowed down to the diagnosis of sepsis in adults. We excluded animal studies, studies limited to single pathogens, or if insufficient data for performance analysis were reported. Tissue sources were limited to routinely accessible biological samples, primarily blood, urine, and cerebrospinal fluid. Biopsies from various solid organs that are not collected as part of routine clinical care were excluded. No restrictions on language or human/animal population were applied to the initial search, although only English language articles on humans were included in the final analysis.

No restrictions were placed on study design type; review articles, editorials, and conference abstracts were excluded.

Utilizing a reference management system (Covidence systematic review software, Veritas Health Innovation, Melbourne, VIC, Australia), publications were retrieved and independently screened for inclusion by at least two investigators (M.V.L., T.M.N., S.T.T.), initially by title and abstract and subsequently by full text. Decisions for inclusion or exclusion were made independently, and any disagreements resolved by discussion. A third reviewer (J.H.L., D.O.) was sought for adjudication in cases where consensus could not be reached.

Data Extraction

Study level data extracted included population demographics, sample size, study design, tissue specimen, type of transcriptome, and health status of comparator group. Data pertaining to performance of the transcriptome collected were: area under the receiver operating characteristic curve (AUC) with 95% CI, true positives, true negatives, false positives, and false negatives where available. Missing data were sought from corresponding authors of included studies by email. Study design was assigned based on a published algorithm for classification of studies (19).

Database studies tend to aggregate public datasets for in silico analysis. As a result, the same dataset of patient transcriptomic data may be reused and published more than once. Studies with duplicated patients were excluded, and where there was overlap, studies with larger sample sizes or more recent studies were preferentially chosen. Where studies report more than one biomarker, only the top three best-performing transcripts are presented in this review, and only the top performing biomarker is subsequently included in the meta-analysis.

Data Synthesis

For diagnostic accuracy analyses, pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratios with corresponding 95% CI were calculated using random-effects model. To synthesize diagnostic precision across multiple studies, the hierarchical summary receiver operating characteristic curves were also computed. I^2 statistics was used to quantify heterogeneity across studies, and an I^2 statistic of 80% or more was considered to indicate considerable heterogeneity. However, owing to the broad review question resulting in an inherently heterogeneous population among included studies, we accepted I^2 statistics up to 95% for inclusion in the meta-analysis. Recognized standards for interpretation of the discriminatory ability of AUC scores are as follows: AUC greater than or equal to 0.90 represents "excellent discrimination," AUC 0.80–0.89 provides "good discrimination," AUC 0.70–0.79 has "minimal discrimination," and AUC less than 0.70 has "poor discrimination" (20–22). A sum of sensitivity and specificity exceeding 1.5 has been recommended as a minimum metric to be reached in order for a test to be considered useful (23). To investigate the heterogeneity in the sensitivity and specificity of different types of control as assigned by the health status of control group, subgroup analyses were performed. Separate subgroup analyses were also performed for transcriptomic biomarkers for the diagnosis of sepsis, clinical definition of sepsis used, number of transcripts used for biomarker diagnosis, and type of transcript (mRNA or ncRNA). All meta-analysis was performed using DerSimonian-Laird random-effects model. Pooled AUC with 95% CI were generated and reported in the forest plot. The statistical analysis for diagnostic accuracy was performed using Meta-DiSc 2.0 (Hospital Ramon y Cajal and Universidad Complutense de Madrid, Madrid, Spain) and Stata V16.0 (StataCorp LLC, College Station, TX).

Risk of Bias Assessment

The risk of bias and quality of the included studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) for observational studies (24), and the Cochrane risk-of-bias tool 2 for randomized trials (25). There are four key domains in the QUADAS-2 tool, namely patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and all the domains apart from flow and timing, are further assessed for their applicability. Assessors are guided by signaling questions, which were adapted to this review, to reach a classification of "high," "low," or "unclear" for each subsection. The risk of bias or applicability was deemed to be "low risk" if all responses to signaling questions in that domain were affirmative;

a classification of "high risk" was given if there were answers in the negative. If any question could not be answered due to lack of information in the included study, the outcome for that subsection was "unclear."

RESULTS

Our literature search identified a total of 11,836 studies. After the removal of 3514 duplicate articles and abstract screening, 1630 full-text articles were assessed for eligibility. Manual searching of review articles and references quoted in relevant articles yielded seven articles. There were a total of 91 database studies identified, of which 11 were included in the final analysis after studies with overlapping datasets, duplicate articles, pediatric subjects, and prognostic objective were removed. Thereafter, a total of 117 studies met the criteria for final inclusion in this review (**Fig. 1**).

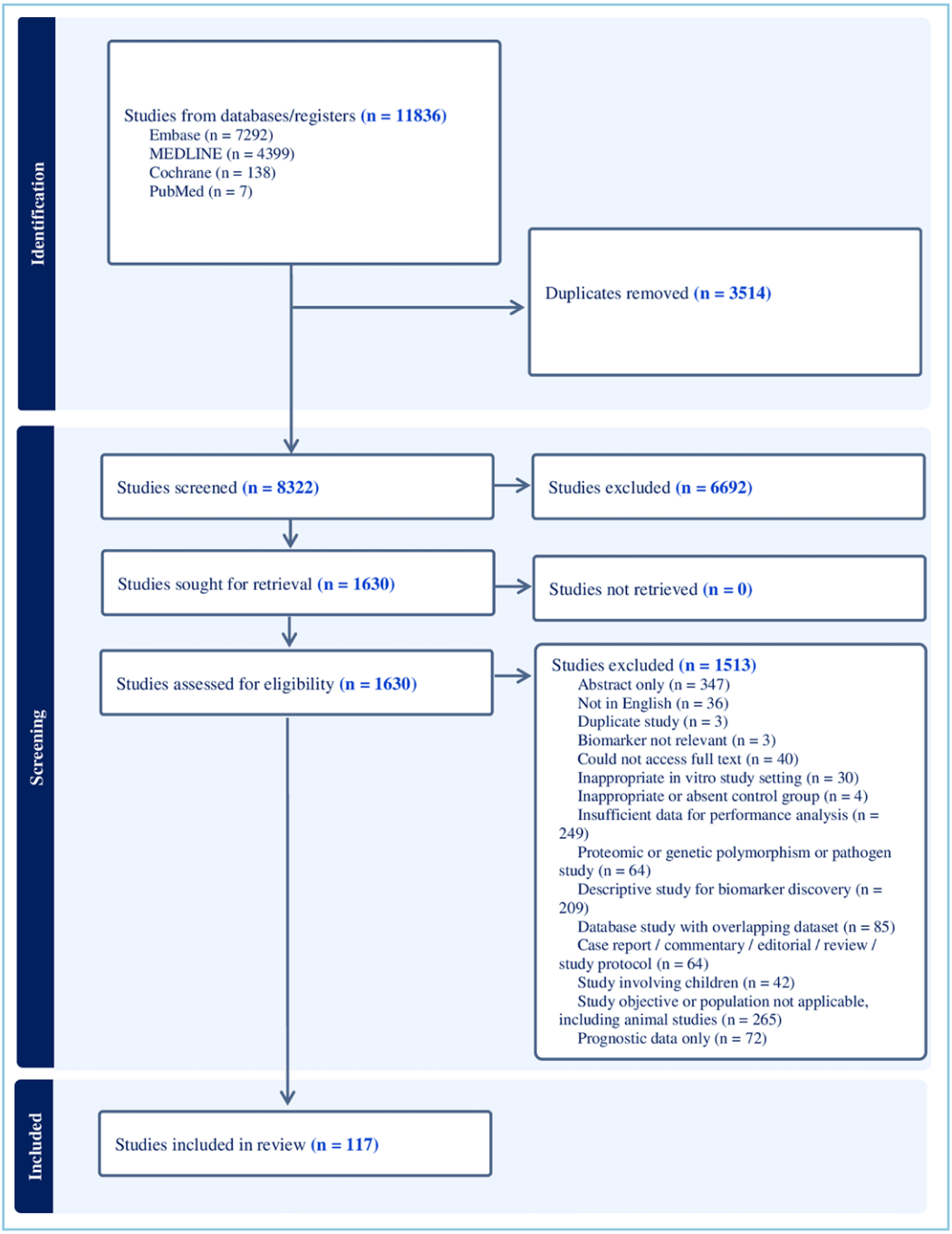

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of results of search.

Diagnosis of Sepsis

A total of 117 studies (n = 17,469 patients; sepsis: 9,874 patients, control: 7,595 patients), comprising 132 patient datasets, reported relevant data for sepsis diagnosis in adults (**Table S1**, http://links.lww.com/CCX/B464). Eleven were analyses of previously unpublished transcriptomic data from public databases, comprising 13 datasets. Patients were adults with sepsis associated with a variety of infections, with only four studies specifying a primary organ system of infection (pneumonia [26, 27], abdominal sepsis [28], and a mix of fecal peritonitis and pneumonia [29]). All the studies were case-controls, with healthy controls being the most commonly used comparator (71 patient datasets). Other control groups used include noninfectious systemic inflammatory response syndrome (SIRS), postoperative,

critically ill without sepsis, and infections without fulfilling clinical sepsis criteria (Table S1, http://links.lww.com/CCX/B464).

Ninety-seven datasets utilized Sepsis-1 (30), -2 (31), or -3 (32) consensus guidelines for case definition, with 35 datasets either not explicitly specifying the source of their inclusion criteria or using different guidelines (33–45). Fifty-two datasets used Sepsis-3 criteria either solely or in combination with other guidance (e.g., Sepsis-1 or Sepsis-2). All studies used blood components (plasma/serum, leukocytes) for analysis; two studies used urine samples (46, 47). Specimen samples were collected within 24–48 hours of admission in all cases where collection procedure was specified. All datasets used reverse transcription quantitative polymerase chain reaction (RT-qPCR) for RNA identification, apart from 14 using microarrays (29, 46–58), four using RNA sequencing technology (59–62), two studies using TaqMan (Thermo Fisher Scientific, Waltham, MA) gene expression assays (33, 63), two using droplet digital polymerase chain reaction (64, 65), and one using a combination of RT-qPCR and microarrays (66).

The most common transcript for single biomarker studies was microRNA (40 datasets). Five studies used dual-microRNA transcripts, and a further four studies used a ratio of microRNA and long ncRNA (lncRNA) due to their endogenous relationship. Single mRNAs were used in 24 datasets, and lncRNAs in 23 datasets. Multiple gene signature transcripts were used in 34 datasets.

Of the 126 study datasets with AUC data, 55 (43%) had excellent discriminatory ability for sepsis diagnosis (AUC ≥ 0.90), 44 (35%) had good ability (ACU 0.80–0.89), 22 (17%) had minimal ability (AUC 0.70–0.79), and five (4%) had poor ability (AUC < 0.70). Among the 73 study datasets with sensitivity and specificity data, 56 (77%) qualified as "useful," as defined by a sum of sensitivity and specificity exceeding 1.5. A meta-analysis of AUCs included 74 datasets, comprising 7036 patients with sepsis and 5303 without sepsis. Pooled AUC was 0.86 (95% CI, 0.84–0.88) (**Fig. S2*a***, http://links.lww.com/CCX/B464). The meta-analysis of sensitivity and specificity included 67 patients' datasets, comprising a total of 5581 patients with sepsis and 4783 without sepsis. Pooled sensitivity was 0.82 (95% CI, 0.79–0.85) and specificity was 0.84 (95% CI, 0.81–0.86) (**Table 1**; **Fig. 2**; and **Fig. S2*b***, http://links.lww.com/CCX/B464).

Subgroup Analysis

Meta-analysis of studies using healthy controls showed AUC 0.87 (95% CI, 0.84–0.89) (38 patient datasets comprising 4541 sepsis patients, 3477 healthy controls) (Table 1; **Fig. 3**; and **Fig. S3**, ***a*** and ***b***, http://links.lww.com/CCX/B464). This compared with AUC 0.84 (95% CI, 0.78–0.90) (ten patient datasets comprising 985 sepsis patients; 481 SIRS controls) when the control population had SIRS (Table 1; Fig. 3; and Fig. S3, *a* and *b*, http://links.lww.com/CCX/B464). Ability to discriminate sepsis from controls comprising critically ill, nonseptic subjects showed AUC 0.77 (95% CI, 0.73–0.81) (Fig. 3; and Fig. S3, *a* and *b*, http://links.lww.com/CCX/B464). Studies that used control subjects with infections without sepsis showed AUC 0.84 (95% CI, 0.71–0.97) (Table 1; Fig. 3; and Fig. S3, *a* and *b*, http://links.lww.com/CCX/B464).

Analysis according to number of transcripts used for diagnosis of sepsis showed AUC 0.85 (95% CI, 0.83–0.87) for single transcripts, AUC 0.88 (95% CI, 0.84–0.93) for dual transcripts, and AUC 0.90 (95% CI, 0.87–0.93) for three or more transcripts (**Table S2** and **Fig. S4**, http://links.lww.com/CCX/B464). Studies using ncRNA transcripts showed AUC 0.86 (95% CI, 0.83–0.88), whereas studies using mRNA transcripts had AUC 0.86 (95% CI, 0.82–0.90) (**Table S3**, http://links.lww.com/CCX/B464). Studies using Sepsis-2 definitions showed AUC 0.81 (95% CI, 0.70–0.91) for healthy controls and AUC 0.79 (95% CI, 0.65–0.94) when controls with SIRS were used. This compared with AUC 0.92 (95% CI, 0.91–0.93) for healthy controls and AUC 0.75 (95% CI, 0.52–0.98) for SIRS controls in studies where Sepsis-3 definitions were used (Table 1; and **Fig. S5*a*–*c***, http://links.lww.com/CCX/B464).

Risk of Bias

QUADAS-2 was used (**Fig. S6**, ***a*** and ***b***, http://links.lww.com/CCX/B464) for assessment of methodological quality and risk of bias (106 studies). For patient selection, 38 (36%) studies were deemed at high risk of bias, with 68 (64%) having insufficient information. The high risk of bias was predominantly because of case-control study design. One hundred four (98%) of the studies were at high risk for bias of the index test because gene transcripts were often chosen based on analysis of differentially expressed genes (DEGs) in

TABLE 1.

Comparison of Meta-Analysis of Diagnostic Accuracy for Patients With Sepsis Versus Different Comparators

Summary Statistic	Healthy (95% CI)	Critically Ill Nonsepsis (95% CI)	Infection Without Sepsis (95% CI)	Postoperative (95% CI)	Systemic Inflammatory Response Syndrome (95% CI)	Overall (95% CI)
All sepsis						
Sensitivity	81.23 (75.98–85.55)	81.1 (59.5–92.6)	84.1 (66.9–93.3)	94.8 (81.7–98.7)[a]	76.50 (65–85)[a]	82.27 (78.82–85.27)
Specificity	84.98 (81.73–87.75)	68.4 (49.7–82.6)[a]	86.8 (74.1–93.8)	77.5 (61.1–88.3)	80.7 (71.6–87.4)	83.65 (80.86–86.10)
DOR	24.49 (16.93–35.41)	9.3 (2.7–31.98)	34.94 (9.88–123.6)	62.43 (13.76–283.26)	13.6 (6.7–27.61)	23.75 (18.12–31.12)
LR+	5.41 (4.42–6.62)	2.57 (1.49–4.44)	6.38 (3.06–13.31)	4.21 (2.3–7.71)	3.96 (2.62–5.99)	5.03 (4.29–5.90)
LR–	0.22 (0.17–0.28)	0.28 (0.12–0.66)	0.18 (0.08–0.41)	0.07 (0.02–0.25)	0.29 (0.19–0.45)	0.21 (0.18–0.25)
AUC	0.87 (0.84–0.89)	0.77 (0.73–0.81)	0.84 (0.71–0.97)	0.92 (0.91–0.93)	0.84 (0.78–0.90)	0.86 (0.83–0.88)
Sepsis-1						
Sensitivity	80.1 (62.4–90.6)			95.7 (70.6–99.5)	77.0 (62.3–87.1)	80.69 (71.96–87.19)
Specificity	82.5 (71.8–89.7)			76.9 (53.3–90.7)	85.3 (75.5–91.6)	82.77 (76.01–87.92)
DOR	18.88 (10.18–35.01)			74.06 (10.72–511.63)	19.36 (9.15–40.94)	20.07 (12.69–31.75)
LR+	4.57 (3.06–6.81)			4.15 (1.9–9.05)	5.22 (3.17–8.6)	4.68 (3.44–6.38)
LR–	0.24 (0.13–0.46)			0.06 (0.01–0.42)	0.27 (0.16–0.45)	0.23 (0.16–0.34)
AUC	0.81 (0.75–0.87)				0.81 (0.75–0.87)	
Sepsis-2						
Sensitivity	73 (59.6–83.1)		90.2 (72.3–97)			80.71 (71.03–87.72)
Specificity	84 (78.4–88.3)		84.9 (70.6–93)			81.22 (75.81–85.65)
DOR	14.12 (6.34–31.44)		51.69 (9.59–278.75)			18.10 (9.54–34.34)
LR+	4.55 (3.08–6.73)		5.98 (2.79–12.86)			4.30 (3.23–5.73)
LR–	0.32 (0.2–0.51)		0.12 (0.04–0.37)			0.24 (0.15–0.37)
AUC	0.81 (0.70–0.91)		0.83 (0.77–0.89)		0.79 (0.65–0.94)	

(*Continued*)

TABLE 1. (*Continued*)
Comparison of Meta-Analysis of Diagnostic Accuracy for Patients With Sepsis Versus Different Comparators

Summary Statistic	Healthy (95% CI)	Critically Ill Nonsepsis (95% CI)	Infection Without Sepsis (95% CI)	Postoperative (95% CI)	Systemic Inflammatory Response Syndrome (95% CI)	Overall (95% CI)
Sepsis-3						
Sensitivity	84.9 (81.1–88.1)	68.4 (49.7–82.6)[a]	68.2 (43.1–85.90)			83.04 (78.38–86.87)
Specificity	87.1 (82–90.9)	70.8 (45.7–87.4)	90.33 (71.32–97.20)			85.97 (80.92–89.85)
DOR	37.93 (25.41–56.61)	5.24 (1.76–15.62)	20.04 (2.51–160.21)			30.01 (18.7–48.18)
LR+	6.56 (4.72–9.13)	2.34 (1.15–4.74)	7.05 (1.74–28.66)			5.92 (4.30–8.15)
LR–	0.17 (0.14–0.22)	0.45 (0.26–0.76)	0.35 (0.16–0.77)			0.20 (0.15–0.25)
AUC	0.92 (0.91–0.93)				0.75 (0.52–0.98)	

AUC = area under the receiver operating characteristic curve, DOR = diagnostic odds ratio, LR– = negative likelihood ratio, LR+ = positive likelihood ratio.
[a]$p < 0.05$ when compared with healthy control.

Figure 2. Summary receiver operating characteristic (SROC) curve of transcriptomics for diagnosis of sepsis in adults.

cases who fulfilled sepsis criteria. Risk of bias were low for reference standard (100 studies, 94% low risk) and flow and timing (81 studies, 76% low risk); concern regarding applicability in terms of patient selection and index test were low throughout. However, risk of bias was high for applicability of the reference standard, as current clinical sepsis criteria perform suboptimally as a gold standard (67).

DISCUSSION

Our review described the performance of a wide variety of transcripts for sepsis diagnosis in adults. Most studies were able to diagnose sepsis with good accuracy. Almost all the studies found distinct host gene expression signatures within 24 hours of sepsis diagnosis or hospital admission, with one study showing ability for diagnosis presymptomatically (68). We did not restrict pathogen cause to a single class since all types of pathogens have potential to cause sepsis, as highlighted by COVID-19.

Overall, our meta-analysis for the performance of transcriptomics for sepsis diagnosis against a pooled cohort of all controls, showed AUC 0.86 (95% CI, 0.84–0.88) (Table 1; and Fig. S2, *a* and *b*, http://links.lww.com/CCX/B464). This pooled AUC shows "good discrimination" (20–22), and the sensitivity and specificity

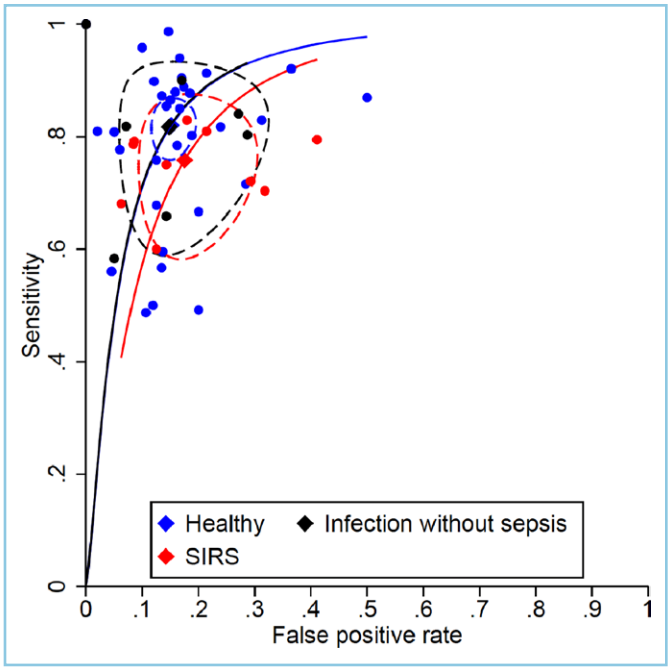

Figure 3. Summary receiver operating characteristic curve for diagnosis of sepsis based on diagnosis of control population. SIRS = systemic inflammatory response syndrome.

meet the threshold for "usefulness" in a diagnostic test (23). However, 71 of 132 (54%) included datasets comprise "healthy" controls, which may less valuable since the clinical challenge is in distinguishing sepsis from other conditions that may present similarly, for example, SIRS. Subgroup analysis showed AUC 0.87 (95% CI, 0.84–0.89) for healthy controls and AUC 0.84 (95% CI, 0.78–0.90) for SIRS controls. Transcriptomics therefore performed well in these patient subgroups, achieving "good discrimination." Further, 13 of 19 patient datasets (68%) (36, 41, 47, 69–74) evaluating transcriptomics for diagnosis of adult sepsis compared with SIRS controls, and which had AUC data, had AUCs of at least 0.8. The biomarkers in common use for the identification of sepsis, namely C-reactive protein (CRP), interleukin-6 (75), and procalcitonin (76) are hampered by poor sensitivity and specificity. Previously published data showed CRP could distinguish sepsis from SIRS with AUC 0.7–0.8 (15, 77, 78), while procalcitonin showed AUC 0.78 (79). In our study, transcriptomics has therefore shown potential for better discrimination of sepsis from SIRS patients than biomarkers in current use.

Further analysis demonstrated improved performance with increasing number of transcripts used. Of the included studies that published data on single vs. dual biomarker use, combining two markers within a study resulted in better diagnostic performance (80–83). A multimarker biosignature may be advantageous in complex diseases such as sepsis, where pathophysiology is complex and data are nonlinear (84). The Sepsis-3 subgroup had higher AUC with healthy controls, but lower AUC with SIRS controls when compared with Sepsis-2. One would expect Sepsis-3 patients to have a more pronounced transcriptomic signal, as only sicker patients will meet the criteria. However, the AUC for SIRS patients using Sepsis-3 was limited by the small number of qualifying studies.

Our systematic review has several strengths. To our knowledge, this is the first published systematic review of transcriptomics for the diagnosis of sepsis. There were a large number of studies and patients included (117 studies comprising 17,469 patients). We did not limit articles by pathogen class, thereby representing the whole spectrum of microbiological causes. We did not exclude patients with preexisting immunodeficiency, as these patients are particularly vulnerable to sepsis with poor outcomes. We have included database studies (**Table S4**, http://links.lww.com/CCX/B464) and have used descriptive statistics to find patterns in the performance of transcriptomics in sepsis, thereby tapping into the large amount of transcriptomic data residing in public repositories.

There are limitations to a systematic review of transcriptomics. First, such a review can only comment on the transcriptome approach as a whole. There is much disparity in performance among the various studies, stemming from methodology (technological and analytical) and choice of transcripts. Hence while this review demonstrates the potential of transcriptomic technology for sepsis diagnosis, biomarker performance rests on the specific transcriptomic test signature chosen. Second, discovery studies and case-control design can lead to overfitting and lack of generalizability (85). Seventy-seven (66%) of the included studies were discovery and/or validation studies for new transcripts. The aforementioned public databases are an excellent resource for validation. We were limited by the data reported by study groups for our analysis—raw data for populating two by two tables for statistical analysis was rarely available, with AUCs being the predominant mode of presenting data. Where 95% CIs were not available, these datasets were not included in the meta-analysis. The majority of controls used were

healthy—this may exaggerate the transcriptomic difference—and may have reduced clinical significance in practice as the diagnostic dilemma is differentiation from disease states mimicking sepsis. Sepsis definitions that were used varied among the different studies, reflecting the iterative change to consensus criteria over the years. Finally, ethnicity may affect interpretation of gene expression studies (86), which is important to note since 69 of 117 studies (59%) included in this review were performed in China. We also had to exclude 36 studies that were not in the English language, most of which were in Chinese.

Implications for Clinical Practice

The difficulty of diagnosing sepsis has led to the adoption of initiatives such as Martha's rule (87). Early and accurate recognition of sepsis, thereby allowing timely intervention are crucial for optimizing outcomes (12, 13, 88). Our study points to a valuable role for transcriptomic biomarkers in the diagnosis of clinical sepsis in adults and demonstrates utility in differentiating sepsis from various clinical conditions. The commonest clinical diagnostic dilemma is in differentiating sepsis from SIRS, and we therefore recommend use of the biosignatures in our SIRS subgroup analysis that showed excellent discriminatory ability according to AUC. These were UrSepsisModel (46), the 210 DEGs described by Denny et al (71), microRNA-143 (72), and Septicyte laboratory (36). Septicyte laboratory (four gene classifier) showed good discriminatory ability for diagnosing sepsis from postoperative patient controls (AUC, 0.89), and minimal to excellent ability when patients with SIRS were used (AUC, 0.77, 0.85, 0.92, 0.93, 0.95) (36). These tests were administered early in the disease course; sepsis is temporally dynamic (29, 89) with evolving immune up-regulation and immunosuppression and changing DEGs (90, 91); hence, the timing of the test is important. Various commercial transcriptomic tests for sepsis are already in development, including Triverity (Inflammatix, Sunnyvale, CA)) and SeptiCyte laboratory (Immunexpress, Seattle, WA), with SeptiCyte RAPID receiving U.S. Food and Drug Administration clearance as a molecular diagnostic test for sepsis.

Unlike other "-omics" approaches, transcriptomics evaluates both up-regulated and down-regulated transcripts, the latter of which has been shown to augment diagnosis (69). Additionally, ncRNAs have a post-transcriptional effect on mRNAs to moderate translation (92), adding a further dimension to diagnostic ability. Combining other modalities such as procalcitonin with transcriptomics could improve diagnostic performance (93) and a comprehensive approach to diagnosis might include conventional biomarkers, metabolic/proteomic markers, and clinical warning scores to improve performance.

Implications for Research

Our review provides a list of performance results for transcripts in various subgroups. This data can guide clinicians on choice of transcripts for clinical use, as well as for researchers designing novel multitranscript biosignatures.

Functional analysis performed on patterns of gene expression using databases such as the Database for Annotation, Visualization, and Integrated Discovery, as well as protein-protein interactions, may shed light on pathophysiological processes (94). Articles in this review provided information on various mediators and pathophysiological pathways in sepsis, including autophagy/apoptosis (45, 95–97), oxidative stress (98), nitric oxide synthase (73, 99), nuclear factor kappa B (38, 100), steroid metabolism (101), metabolic and immune modulation (46, 47, 56, 60, 69, 71, 102–105), and identified potential therapeutic targets (29, 38, 46, 61, 65, 69, 73, 101, 105–109). Further research to elucidate sepsis pathways and identify potential therapeutic targets is needed.

Some included studies reported the use of transcriptomics for prognostication of sepsis including mortality (42, 65, 69, 73, 80, 81, 83, 94, 96, 98, 103, 106, 110–131), as well as specific organ failure such as acute respiratory distress syndrome (45, 100, 132–134), myocardial compromise (44, 53, 102, 108, 135–138), and renal dysfunction (61). Sepsis prognostication is a promising application of transcriptomics, with potential to guide specific therapies and organ support, and warrants further research to evaluate its value. For example, transcriptomic signatures show potential for guiding use of steroids in sepsis (101, 139).

A criticism of earlier consensus sepsis definitions using SIRS criteria was that many patients with milder infections would also qualify. We recommend the use of Sepsis-3 criteria for future clinical transcriptomic research, thereby focusing on the so-called "bad infection" (140). Further

research should focus on clinically relevant controls such as SIRS, including validation of the top performing transcripts in our review, which used healthy controls.

CONCLUSIONS

This review has demonstrated the clinical utility of transcriptomics for the early diagnosis of sepsis, thereby allowing timely intervention to optimize clinical outcomes. Transcriptomics also shows much potential for delineating pathophysiological pathways, and the identification of therapeutic targets.

ACKNOWLEDGMENTS

We thank the invaluable input of Matthew Henry, outreach librarian, Bodleian Health Care Libraries, University of Oxford, United Kingdom, for his assistance in formulating the search strategy and retrieving journal articles.

1 *Department of Paediatric Subspecialties, Children's Intensive Care Unit, KK Women's and Children's Hospital, Singapore, Singapore.*

2 *Center for Quantitative Medicine, Duke-NUS Medical School, Singapore, Singapore.*

3 *Department of Industrial Systems Engineering and Management, College of Design and Engineering, National University of Singapore, Singapore, Singapore.*

4 *Department of Biological Sciences, National University of Singapore, Singapore, Singapore.*

5 *SingHealth-Duke NUS Paediatrics Academic Programme, Duke-NUS Medical School, Singapore, Singapore.*

6 *Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, United Kingdom.*

7 *NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

The authors have no potential conflicts of interest or financial disclosures to declare.

Dr. Lee and Dr. O'Connor are joint last authors.

For information regarding this article, E-mail: Mervin.loi.v.t@singhealth.com.sg

REFERENCES

1. Jarczak D, Kluge S, Nierhaus A: Sepsis-pathophysiology and therapeutic concepts. *Front Med (Lausanne)* 2021; 8:628302
2. van den Berg M, van Beuningen FE, Ter Maaten JC, et al: Hospital-related costs of sepsis around the world: A systematic review exploring the economic burden of sepsis. *J Crit Care* 2022; 71:154096
3. Fleischmann C, Scherag A, Adhikari NK, et al; International Forum of Acute Care Trialists: Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016; 193:259–272
4. Hotchkiss RS, Moldawer LL, Opal SM, et al: Sepsis and septic shock. *Nat Rev Dis Primers* 2016; 2:16045
5. Boomer JS, Green JM, Hotchkiss RS: The changing immune system in sepsis: Is individualized immuno-modulatory therapy the answer? *Virulence* 2014; 5:45–56
6. Cruz DN, Antonelli M, Fumagalli R, et al: Early use of polymyxin B hemoperfusion in abdominal septic shock: The EUPHAS randomized controlled trial. *JAMA* 2009; 301:2445–2452
7. Payen DM, Guilhot J, Launey Y, et al; ABDOMIX Group: Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: A multicenter randomized control trial. *Intensive Care Med* 2015; 41:975–984
8. Lai PS, Thompson BT: Why activated protein C was not successful in severe sepsis and septic shock: Are we still tilting at windmills? *Curr Infect Dis Rep* 2013; 15:407–412
9. Levy MM, Rhodes A, Phillips GS, et al: Surviving sepsis campaign: Association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015; 43:3–12
10. Evans L, Rhodes A, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; 49:e1063–e1143
11. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
12. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
13. Muszynski JA, Knatz NL, Sargel CL, et al: Timing of correct parenteral antibiotic initiation and outcomes from severe bacterial community-acquired pneumonia in children. *Pediatr Infect Dis J* 2011; 30:295–301
14. Rhee C, Jones TM, Hamad Y, et al; Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program: Prevalence, underlying causes, and preventability of sepsis-associated mortality in US acute care hospitals. *JAMA Netw Open* 2019; 2:e187571
15. Castelli GP, Pognani C, Meisner M, et al: Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care* 2004; 8:R234–R242
16. Pelaia TM, Shojaei M, McLean AS: The role of transcriptomics in redefining critical illness. *Crit Care* 2023; 27:89
17. Kelly E, Whelan SO, Harriss E, et al: Systematic review of host genomic biomarkers of invasive bacterial disease: Distinguishing bacterial from non-bacterial causes of acute febrile illness. *EBioMedicine* 2022; 81:104110

18. Page MJ, McKenzie JE, Bossuyt PM, et al: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71
19. Mathes T, Pieper D: An algorithm for the classification of study designs to assess diagnostic, prognostic and predictive test accuracy in systematic reviews. *Syst Rev* 2019; 8:226
20. Nigrovic LE, Bennett JE, Balamuth F, et al; for Pedi Lyme Net: Accuracy of clinician suspicion of Lyme disease in the emergency department. *Pediatrics* 2017; 140:e20171975
21. Bijlsma MW, Brouwer MC, Bossuyt PM, et al: Risk scores for outcome in bacterial meningitis: Systematic review and external validation study. *J Infect* 2016; 73:393–401
22. Muller MP, Tomlinson G, Marrie TJ, et al: Can routine laboratory tests discriminate between severe acute respiratory syndrome and other causes of community-acquired pneumonia? *Clin Infect Dis* 2005; 40:1079–1086
23. Power M, Fell G, Wright M: Principles for high-quality, high-value testing. *Evid Based Med* 2013; 18:5–10
24. Atta L, Fan J: Computational challenges and opportunities in spatially resolved transcriptomic data analysis. *Nat Commun* 2021; 12:5283
25. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928
26. Zhao L: Exploration of values of MiR-7110-5p and MiR-223-3p in predicting sepsis. *Cell Mol Biol (Noisy-le-Grand, France)* 2022; 68:69–73
27. Zhang W, Jia J, Liu Z, et al: Circulating microRNAs as biomarkers for Sepsis secondary to pneumonia diagnosed via Sepsis 3.0. *BMC Pulm Med* 2019; 19:93
28. Scicluna BP, Wiewel MA, Van Vught LA, et al: Molecular biomarker to assist in diagnosing abdominal sepsis upon ICU admission. *Am J Respir Crit Care Med* 2018; 197:1070–1073
29. Burnham KL, Davenport EE, Radhakrishnan J, et al: Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. *Am J Respir Crit Care Med* 2017; 196:328–339
30. Bone RC, Sibbald WJ, Sprung CL: The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest* 1992; 101:1481–1483
31. Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS: 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med* 2003; 31:1250–1256
32. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:801–810
33. Grealy R, White M, Stordeur P, et al: Characterising cytokine gene expression signatures in patients with severe sepsis. *Mediators Inflamm* 2013; 2013:164246
34. Liu H, Wang SY, Li XD, et al: The expression of TRPM7 in serum of patients with sepsis, its influences on inflammatory factors and prognosis, and its diagnostic value. *Eur Rev Med Pharmacol Sci* 2019; 23:3926–3932
35. Liu Q, Wang Y, Zheng Q, et al: MicroRNA-150 inhibits myeloid-derived suppressor cells proliferation and function through negative regulation of ARG-1 in sepsis. *Life Sci* 2021; 278:119626
36. McHugh L, Seldon TA, Brandon RA, et al: A molecular host response assay to discriminate between sepsis and infection-negative systemic inflammation in critically ill patients: Discovery and validation in independent cohorts. *PLoS Med* 2015; 12:e1001916
37. Pan X, He L: LncRNA MEG3 expression in sepsis and its effect on LPS-induced macrophage function. *Cell Mol Biol (Noisy-le-Grand, France)* 2020; 66:131–136
38. Sun X, Icli B, Wara AK, et al; MICU Registry: MicroRNA-181b regulates NF-kappaB-mediated vascular inflammation. *J Clin Invest* 2012; 122:1973–1990
39. Wang HF, Li Y, Wang YQ, et al: MicroRNA-494-3p alleviates inflammatory response in sepsis by targeting TLR6. *Eur Rev Med Pharmacol Sci* 2019; 23:2971–2977
40. Wang J-f, M-l Y, Yu G, et al: Serum miR-146a and miR-223 as potential new biomarkers for sepsis. *Biochem Biophys Res Commun* 2010; 394:184–188
41. Wang L, Wang H-C, Chen C, et al: Differential expression of plasma miR-146a in sepsis patients compared with non-sepsis-SIRS patients. *Exp Ther Med* 2013; 5:1101–1104
42. Xu C, Zhou G, Wang X, et al: Correlation analysis of serum miR-21 and miR-210 with hs-CRP, TNF-α, IL-6, and ICAM-1 in patients with sepsis after burns. *Burns* 2022; 48:633–638
43. Yu B, Cui R, Lan Y, et al: Long non-coding RNA H19 as a diagnostic marker in peripheral blood of patients with sepsis. *Am J Transl Res* 2021; 13:2923–2930
44. Zhou W, Yu C, Long Y: Myo-inositol oxygenase (MIOX) accelerated inflammation in the model of infection-induced cardiac dysfunction by NLRP3 inflammasome. *Immun Inflammation Dis* 2023; 11:e829
45. Zhou Y, Sun L, Zhu M, et al: Effects and early diagnostic value of lncRNA H19 on sepsis-induced acute lung injury. *Exp Ther Med* 2022; 23:279
46. Bandyopadhyay S, Loftus TJ, Peng Y-C, et al: Early differentiation between sepsis and sterile inflammation via urinary gene signatures of metabolic dysregulation. *Shock* 2022; 58:20–27
47. Bandyopadhyay S, Lysak N, Adhikari L, et al: Discovery and validation of urinary molecular signature of early sepsis. *Crit Care Explor* 2020; 2:e0195
48. Yang Y, Zhang Y, Li S, et al: A robust and generalizable immune-related signature for sepsis diagnostics. *IEEE/ACM Trans Comput Biol Bioinf* 2022; 19:3246–3254
49. She H, Hu Y, Zhou Y, et al: Protective effects of dexmedetomidine on sepsis-induced vascular leakage by alleviating ferroptosis via regulating metabolic reprogramming. *J Inflamm Res* 2021; 14:6765–6782
50. Qian W, Zhou J, Shou S: Exploration of m6A methylation regulators as epigenetic targets for immunotherapy in advanced sepsis. *BMC Bioinf* 2023; 24:257
51. Lu J, Li Q, Wu Z, et al: Two gene set variation indexes as potential diagnostic tool for sepsis. *Am J Transl Res* 2020; 12:2749–2759
52. Li H, Wang X, Yang Q, et al: Identification of iron metabolism-related genes as diagnostic signatures in sepsis by blood transcriptomic analysis. *Open Life Sci* 2023; 18:20220549
53. Hu Y, Cheng L, Zhong W, et al: Bioinformatics analysis of gene expression profiles for risk prediction in patients with septic shock. *Med Sci Monit* 2019; 25:9563–9571

54. Fu M, Zhang K: MAPK interacting serine/threonine kinase 1 (MKNK1), one target gene of miR-223-3p, correlates with neutrophils in sepsis based on bioinformatic analysis. *Bioengineered* 2021; 12:2550–2562
55. Chen Y, Wang X, Wang J, et al: Revealing novel pyroptosis-related therapeutic targets for sepsis based on machine learning. *BMC Med Genomics* 2023; 16:23
56. Tang BMP, McLean AS, Dawes IW, et al: The use of gene-expression profiling to identify candidate genes in human sepsis. *Am J Respir Crit Care Med* 2007; 176:676–684
57. Tang BMP, McLean AS, Dawes IW, et al: Gene-expression profiling of peripheral blood mononuclear cells in sepsis. *Crit Care Med* 2009; 37:882–888
58. Maslove DM, Shapira T, Tyryshkin K, et al: Validation of diagnostic gene sets to identify critically ill patients with sepsis. *J Crit Care* 2019; 49:92–98
59. Mo Q, Mo Q, Mo F: Single-cell RNA sequencing and transcriptomic analysis reveal key genes and regulatory mechanisms in sepsis. *Biotechnol Genet Eng Rev* 2023; 40:1636–1658
60. Reyes M, Filbin MR, Bhattacharyya RP, et al: An immune-cell signature of bacterial sepsis. *Nat Med* 2020; 26:333–340
61. Pena OM, Hancock DG, Lyle NH, et al: An endotoxin tolerance signature predicts sepsis and organ dysfunction at initial clinical presentation. *EBioMedicine* 2014; 1:64–71
62. Kalantar KL, Neyton L, Abdelghany M, et al: Integrated host-microbe plasma metagenomics for sepsis diagnosis in a prospective cohort of critically ill adults. *Nat Microbiol* 2022; 7:1805–1816
63. Möhnle P, Hirschberger S, Hinske LC, et al: MicroRNAs 143 and 150 in whole blood enable detection of T-cell immunoparalysis in sepsis. *Mol Med* 2018; 24:54
64. Link F, Krohn K, Burgdorff AM, et al: Sepsis diagnostics: Intensive care scoring systems superior to microRNA biomarker testing. *Diagnostics (Basel)* 2020; 10:701
65. Almansa R, Ortega A, Avila-Alonso A, et al: Quantification of immune dysregulation by next-generation polymerase chain reaction to improve sepsis diagnosis in surgical patients. *Ann Surg* 2019; 269:545–553
66. Sun M, Yang Q, Hu C, et al: Identification and validation of autophagy-related genes in sepsis-induced acute respiratory distress syndrome and immune infiltration. *J Inflamm Res* 2022; 15:2199–2212
67. Sartelli M, Kluger Y, Ansaloni L, et al: Raising concerns about the Sepsis-3 definitions. *World J Emerg Surg* 2018; 13:6
68. Lukaszewski RA, Jones HE, Gersuk VH, et al: Presymptomatic diagnosis of postoperative infection and sepsis using gene expression signatures. *Intensive Care Med* 2022; 48:1133–1143
69. Bauer M, Giamarellos-Bourboulis EJ, Kortgen A, et al: A transcriptomic biomarker to quantify systemic inflammation in sepsis—a prospective multicenter phase II diagnostic study. *EBioMedicine* 2016; 6:114–125
70. Caserta S, Kern F, Cohen J, et al: Circulating plasma microRNAs can differentiate human sepsis and systemic inflammatory response syndrome (SIRS). *Sci Rep* 2016; 6:28006
71. Denny KJ, Lea RA, Lindell-Innes R, et al: Diagnosing sepsis in the ICU: Comparison of a gene expression signature to pre-existing biomarkers. *J Crit Care* 2023; 76:154286
72. Han Y, Dai Q-C, Shen H-L, et al: Diagnostic value of elevated serum miRNA-143 levels in sepsis. *J Int Med Res* 2016; 44:875–881
73. Yao L, Liu Z, Zhu J, et al: Clinical evaluation of circulating microRNA-25 level change in sepsis and its potential relationship with oxidative stress. *Int J Clin Exp Path* 2015; 8:7675–7684
74. Wang H, Zhang P, Chen W, et al: Evidence for serum miR-15a and miR-16 levels as biomarkers that distinguish sepsis from systemic inflammatory response syndrome in human subjects. *Clin Chem Lab Med* 2012; 50:1423–1428
75. Trancă SD, Petrişor CL, Hagău N: Biomarkers in polytrauma induced systemic inflammatory response syndrome and sepsis—a narrative review. *Rom J Anaesth Intensive Care* 2014; 21:118–122
76. Sinha M, Desai S, Mantri S, et al: Procalcitonin as an adjunctive biomarker in sepsis. *Indian J Anaesth* 2011; 55:266–270
77. Luzzani A, Polati E, Dorizzi R, et al: Comparison of procalcitonin and C-reactive protein as markers of sepsis. *Crit Care Med* 2003; 31:1737–1741
78. Rey C, Los Arcos M, Concha A, et al: Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. *Intensive Care Med* 2007; 33:477–484
79. Tang BM, Eslick GD, Craig JC, et al: Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: Systematic review and meta-analysis. *Lancet Infect Dis* 2007; 7:210–217
80. He F, Zhang C, Huang Q: Long noncoding RNA nuclear enriched abundant transcript 1/miRNA-124 axis correlates with increased disease risk, elevated inflammation, deteriorative disease condition, and predicts decreased survival of sepsis. *Medicine (Baltimore)* 2019; 98:e16470
81. Na L, Ding H, Xing E, et al: Lnc-MEG3 acts as a potential biomarker for predicting increased disease risk, systemic inflammation, disease severity, and poor prognosis of sepsis via interacting with miR-21. *J Clin Lab Anal* 2020; 34:e23123
82. Trung NT, Lien TT, Sang VV, et al: Circulating miR-147b as a diagnostic marker for patients with bacterial sepsis and septic shock. *PLoS One* 2021; 16:e0261228
83. Yao J, Lui KY, Hu X, et al: Circulating microRNAs as novel diagnostic biomarkers and prognostic predictors for septic patients. *Infect Genet Evol* 2021; 95:105082
84. Brandon RB, Thomas M, Brandon RA, et al: A limited set of molecular biomarkers may provide superior diagnostic outcomes to procalcitonin in sepsis. *Crit Care* 2012; 16(Suppl 3):P40
85. Sweeney TE, Khatri P: Comprehensive validation of the FAIM3:PLAC8 ratio in time-matched public gene expression data. *Am J Respir Crit Care Med* 2015; 192:1260–1261
86. Peck Palmer OM, Rogers G, Yende S, et al: Graph theoretical analysis of genome-scale data: Examination of gene activation occurring in the setting of community-acquired pneumonia. *Shock* 2018; 50:53–59
87. Dyer C: Martha's rule: What could the proposed changes mean for doctors? *BMJ* 2023; 382:2067
88. Weiss SL, Balamuth F, Hensley J, et al: The epidemiology of hospital death following pediatric severe sepsis: When, why, and how children with sepsis die. *Pediatr Crit Care Med* 2017; 18:823–830

89. Balch JA, Chen UI, Liesenfeld O, et al: Defining critical illness using immunological endotypes in patients with and without of sepsis: A cohort study. *Res Sq* 2023
90. Talwar S, Munson PJ, Barb J, et al: Gene expression profiles of peripheral blood leukocytes after endotoxin challenge in humans. *Physiol Genomics* 2006; 25:203–215
91. Tang BM, Huang SJ, McLean AS: Genome-wide transcription profiling of human sepsis: A systematic review. *Crit Care* 2010; 14:R237
92. Antonakos N, Gilbert C, Théroude C, et al: Modes of action and diagnostic value of miRNAs in sepsis. *Front Immunol* 2022; 13:951798
93. Lin X, Wang Y: miR-141 is negatively correlated with TLR4 in neonatal sepsis and regulates LPS-induced inflammatory responses in monocytes. *Braz J Med Biol Res* 2021; 54:e10603
94. Wang H, Feng Q, Wu Y, et al: Association of circulating long non-coding RNA HULC expression with disease risk, inflammatory cytokines, biochemical index levels, severity-assessed scores, and mortality of sepsis. *J Clin Lab Anal* 2021; 35:e23656
95. Chen Z, Zeng L, Liu G, et al: Construction of autophagy-related gene classifier for early diagnosis, prognosis and predicting immune microenvironment features in sepsis by machine learning algorithms. *J Inflamm Res* 2022; 15:6165–6186
96. Miliaraki M, Briassoulis P, Ilia S, et al: Survivin and caspases serum protein levels and survivin variants mRNA expression in sepsis. *Sci Rep* 2021; 11:1049
97. Si X, Cao D, Chen J, et al: miR-23a downregulation modulates the inflammatory response by targeting ATG12-mediated autophagy. *Mol Med Rep* 2018; 18:1524–1530
98. Ou Y, An R, Wang H, et al: Oxidative stress-related circulating miRNA-27a is a potential biomarker for diagnosis and prognosis in patients with sepsis. *BMC Immunol* 2022; 23:14
99. Tsukahara Y, Morisaki T, Horita Y, et al: Expression of inducible nitric oxide synthase in circulating neutrophils of the systemic inflammatory response syndrome and septic patients. *World J Surg* 1998; 22:771–777
100. Chen W, Liu L, Yang J, et al: MicroRNA-146b correlates with decreased acute respiratory distress syndrome risk, reduced disease severity, and lower 28-day mortality in sepsis patients. *J Clin Lab Anal* 2020; 34:e23510
101. Vardas K, Ilia S, Sertedaki A, et al: Increased glucocorticoid receptor expression in sepsis is related to heat shock proteins, cytokines, and cortisol and is associated with increased mortality. *Intensive Care Med Exp* 2017; 5:10
102. Martinez-Paz P, Aragon-Camino M, Gomez-Sanchez E, et al: Distinguishing septic shock from non-septic shock in postsurgical patients using gene expression. *J Infect* 2021; 83:147–155
103. Choi H, Lee JY, Yoo H, et al: Bioinformatics analysis of gene expression profiles for diagnosing sepsis and risk prediction in patients with sepsis. *Int J Mol Sci* 2023; 24:9362
104. Sutherland A, Thomas M, Brandon RA, et al: Development and validation of a novel molecular biomarker diagnostic test for the early detection of sepsis. *Crit Care* 2011; 15:R149
105. Wu T, Liang X, Jiang Y, et al: Comprehensive transcriptome profiling of peripheral blood mononuclear cells from patients with sepsis. *Int J Med Sci* 2020; 17:2077–2086
106. Xu H, Liu X, Ni H: Clinical significance of miR-19b-3p in patients with sepsis and its regulatory role in the LPS-induced inflammatory response. *Eur J Med Res* 2020; 25:9
107. Wang H, Xuan P, Tian H, et al: Adipose-derived mesenchymal stem cell-derived HCAR1 regulates immune response in the attenuation of sepsis. *Mol Med Rep* 2022; 26:279
108. Wang H, Cui W, Qiao L, et al: Overexpression of miR-451a in sepsis and septic shock patients is involved in the regulation of sepsis-associated cardiac dysfunction and inflammation. *Genet Mol Biol* 2020; 43:e20200009
109. Al Mansour N, Al-Kafaji G, Al Mahmeed A, et al: Dysregulation of human beta-defensin-3 expression in the peripheral blood of patients with sepsis. *SAGE Open Med* 2021; 9:20503121211041515
110. Abou El-Khier NT, Zaki ME, Alkasaby NM: Study of microRNA-122 as a diagnostic biomarker of sepsis. *Egypt J Immunol* 2019; 26:105–116
111. Chen L, Yu L, Zhang R, et al: Correlation of microRNA-146a/b with disease risk, biochemical indices, inflammatory cytokines, overall disease severity, and prognosis of sepsis. *Medicine (Baltimore)* 2020; 99:e19754
112. Geng F, Liu W, Yu L: Potential role of circulating long non-coding RNA MALAT1 in predicting disease risk, severity, and patients' survival in sepsis. *J Clin Lab Anal* 2019; 33:e22968
113. Huang Q, Huang C, Luo Y, et al: Circulating lncRNA NEAT1 correlates with increased risk, elevated severity and unfavorable prognosis in sepsis patients. *Am J Emerg Med* 2018; 36:1659–1663
114. Li N, Wu S, Yu L: The associations of long non-coding RNA taurine upregulated gene 1 and microRNA-223 with general disease severity and mortality risk in sepsis patients. *Medicine (Baltimore)* 2020; 99:e23444
115. Lin R, Hu H, Li L, et al: The potential of microRNA-126 in predicting disease risk, mortality of sepsis, and its correlation with inflammation and sepsis severity. *J Clin Lab Anal* 2020; 34:e23408
116. Liu W, Geng F, Yu L: Long non-coding RNA MALAT1/microRNA 125a axis presents excellent value in discriminating sepsis patients and exhibits positive association with general disease severity, organ injury, inflammation level, and mortality in sepsis patients. *J Clin Lab Anal* 2020; 34:e23222
117. Qiu G, Fan J, Zheng G, et al: Diagnostic potential of plasma extracellular vesicle miR-483-3p and Let-7d-3p for sepsis. *Front Mol Biosci* 2022; 9:814240
118. Rahmel T, Schäfer ST, Frey UH, et al: Increased circulating microRNA-122 is a biomarker for discrimination and risk stratification in patients defined by sepsis-3 criteria. *PLoS One* 2018; 13:e0197637
119. Sun B, Guo S: miR-486-5p serves as a diagnostic biomarker for sepsis and its predictive value for clinical outcomes. *J Inflamm Res* 2021; 14:3687–3695
120. Wang R, Zhao J, Wei Q, et al: Potential of circulating lncRNA CASC2 as a biomarker in reflecting the inflammatory cytokines, multi-organ dysfunction, disease severity, and mortality in sepsis patients. *J Clin Lab Anal* 2022; 36:e24569

121. Wei B, Yu L: Circular RNA PRKCI and microRNA-545 relate to sepsis risk, disease severity and 28-day mortality. *Scand J Clin Lab Invest* 2020; 80:659–666
122. Wu X, Yang J, Yu L, et al: Plasma miRNA-223 correlates with risk, inflammatory markers as well as prognosis in sepsis patients. *Medicine (Baltimore)* 2018; 97:e11352
123. Xiao J, Wu Y, Paranggan P, et al: Involvement of plasma lncRNA GSEC in sepsis discrimination and prognosis, and its correlation with macrophage cell inflammation and proliferation. *Immunobiology* 2022; 227:152264
124. Xu Y, Shao B: Circulating long noncoding RNA ZNFX1 antisense RNA negatively correlates with disease risk, severity, inflammatory markers, and predicts poor prognosis in sepsis patients. *Medicine (Baltimore)* 2019; 98:e14558
125. Fang Y, Hu J, Wang Z, et al: LncRNA H19 functions as an Aquaporin 1 competitive endogenous RNA to regulate microRNA-874 expression in LPS sepsis. *Biomed Pharmacother* 2018; 105:1183–1191
126. Zeng Q, Wu J, Yang S: Circulating lncRNA ITSN1-2 is upregulated, and its high expression correlates with increased disease severity, elevated inflammation, and poor survival in sepsis patients. *J Clin Lab Anal* 2019; 33:e22836
127. Zhang W, Chen B, Chen W: LncRNA GAS5 relates to Th17 cells and serves as a potential biomarker for sepsis inflammation, organ dysfunctions and mortality risk. *J Clin Lab Anal* 2022; 36:e24309
128. Zhang X, Dong S: Protective effect of growth differentiation factor 15 in sepsis by regulating macrophage polarization and its mechanism. *Bioengineered* 2022; 13:9687–9707
129. Zhao D, Li S, Cui J, et al: Plasma miR-125a and miR-125b in sepsis: Correlation with disease risk, inflammation, severity, and prognosis. *J Clin Lab Anal* 2020; 34:e23036
130. Zheng G, Qiu G, Ge M, et al: miR-10a in peripheral blood mononuclear cells is a biomarker for sepsis and has anti-inflammatory function. *Mediators Inflamm* 2020; 2020:4370983
131. Zhu X: MiR-125b but not miR-125a is upregulated and exhibits a trend to correlate with enhanced disease severity, inflammation, and increased mortality in sepsis patients. *J Clin Lab Anal* 2020; 34:e23094
132. Wu X, Chen D, Yu L: The value of circulating long non-coding RNA maternally expressed gene 3 as a predictor of higher acute respiratory distress syndrome risk and 28-day mortality in sepsis patients. *J Clin Lab Anal* 2020; 34:e23488
133. Yang Y, Yang L, Liu Z, et al: Long noncoding RNA NEAT 1 and its target microRNA-125a in sepsis: Correlation with acute respiratory distress syndrome risk, biochemical indexes, disease severity, and 28-day mortality. *J Clin Lab Anal* 2020; 34:e23509
134. Zhang C, Huang Q, He F: Correlation of small nucleolar RNA host gene 16 with acute respiratory distress syndrome occurrence and prognosis in sepsis patients. *J Clin Lab Anal* 2022; 36:e24516
135. Chen J, He Y, Zhou L, et al: Long non-coding RNA MALAT1 serves as an independent predictive biomarker for the diagnosis, severity and prognosis of patients with sepsis. *Mol Med Rep* 2020; 21:1365–1373
136. Fan H, Shao H, Gao X: Long non-coding RNA HOTTIP is elevated in patients with sepsis and promotes cardiac dysfunction. *Immunol Invest* 2022; 51:2086–2096
137. Yang C, Wen K: Predictive value and regulatory mechanism of serum miR-499a-5p on myocardial dysfunction in sepsis. *J Cardiothorac Surg* 2021; 16:301
138. Zhang B, Yu L, Sheng Y: Clinical value and role of microRNA-29c-3p in sepsis-induced inflammation and cardiac dysfunction. *Eur J Med Res* 2021; 26:90
139. Antcliffe DB, Burnham KL, Al-Beidh F, et al: Transcriptomic signatures in sepsis and a differential response to steroids. From the VANISH randomized trial. *Am J Respir Crit Care Med* 2019; 199:980–986
140. Vincent JL: Evolution of the concept of sepsis. *Antibiotics (Basel)* 2022; 11:1581