SYSTEMATIC REVIEW

OPEN

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

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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

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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**).

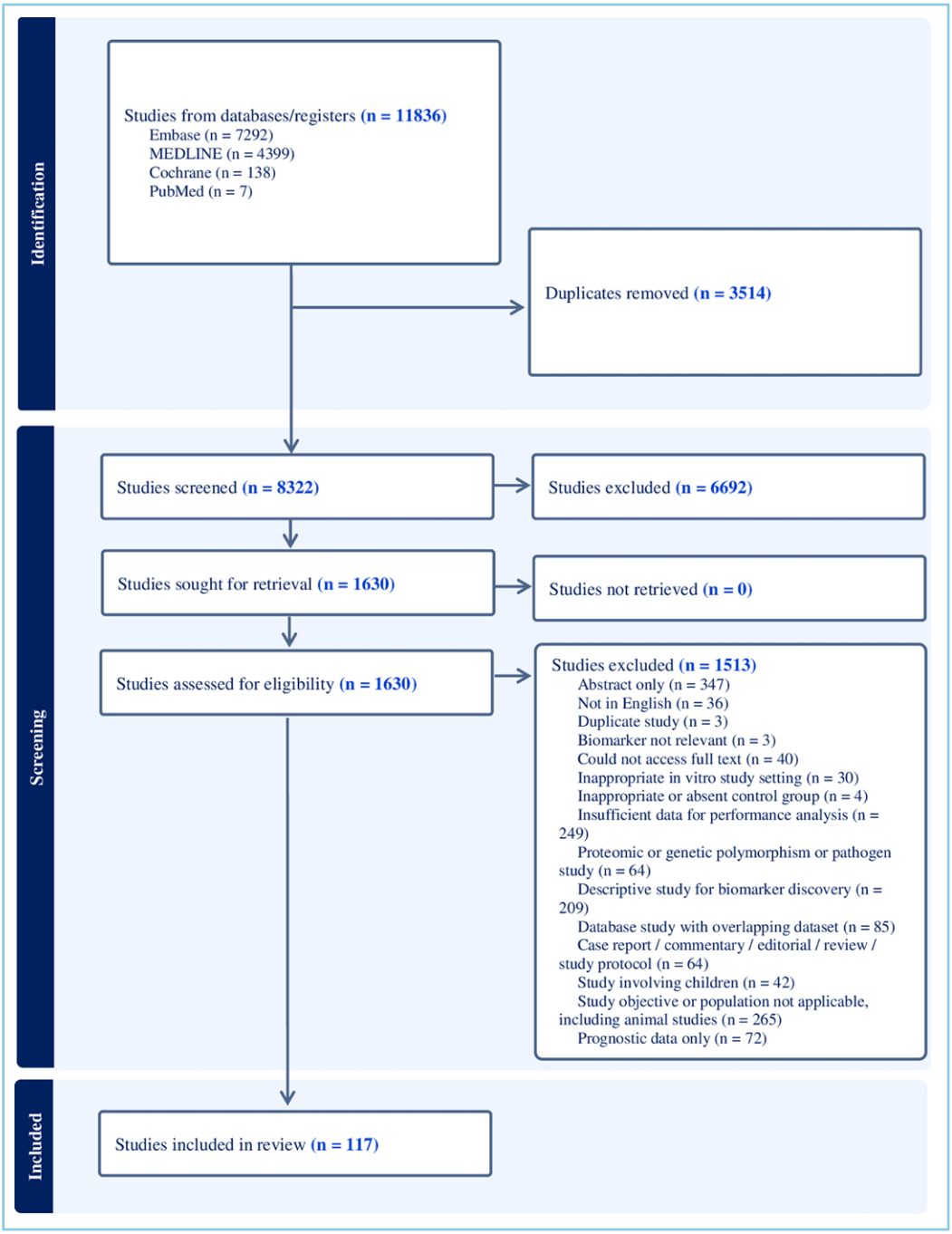

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of results of search.

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

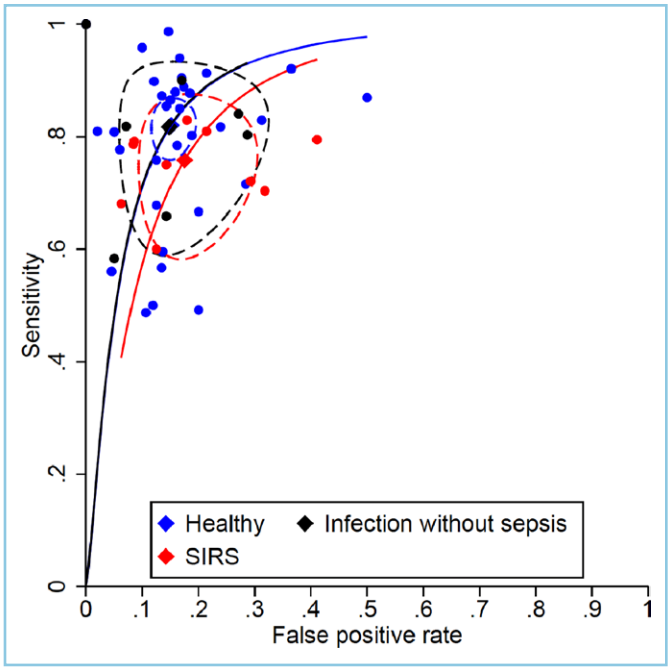

Figure 3. Summary receiver operating characteristic curve for diagnosis of sepsis based on diagnosis of control population. SIRS = systemic inflammatory response syndrome.

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.

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