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Review Article

MicroRNAs as a Diagnostic Tool in Bacterial Infections: A Review Article

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Abstract

Background: Severe sepsis and tuberculosis are major causes of mortality due to infection all over the world. The impact of microRNAs (miRNAs) in activating the immune process during bacterial infections is essential and associated with managing gene expression of inflammatory markers. ***Objective***: To find the available evidence regarding the diagnostic potential and mechanistic utility of total circulating miRNAs and EV-derived miRNAs in human bacterial infections, that is, sepsis and TB. ***Methods***: This study is based on a PRISMA-DTA literature review. In this study, a comprehensive search was conducted on different databases such as PubMed, Embase, Web of Science, and Scopus between 1 January 2013 and 15 February 2025 for papers related to this topic. The risk of bias was assessed by the QUADAS-2 tool. ***Results***: We evaluated 46 records on sepsis, tuberculosis, severe pneumonia, and bacterial meningitis out of 1,319 records. Most of the studies, about 74%, were case-control using 65% serum, 38% plasma, and 82% qRT-PCR. Sepsis circulating microRNAs showed moderate-to-high diagnostic accuracy where miR-155-5p AUC=0.81, miR-223 AUC=0.79, and multi-miRNA panels up to AUC=0.90; severe pneumonia showed miR-155 AUC=0.79, miR-34a AUC=0.81, and miR-150 AUC=0.83; tuberculosis showed miR-29a AUC=0.81 and panels including miR-144 and miR-197 AUC=0.87; and bacterial meningitis showed CSF miR-181a AUC=0.82, plasma miR-223 AUC=0.79, and CSF miR-125b AUC=0.84. ***Conclusions***: MicroRNAs in the circulation have demonstrated moderate-to-high forms of diagnostic accuracy among various bacteria and their infections, such as sepsis, tuberculosis, severe pneumonia, and bacterial meningitis.

Keywords: Bacterial infection; Extracellular vesicles; microRNA; Sepsis; Tuberculosis.

الميكرو RNA كأداة تشخيصية في العدوى البكتيرية: مقال مراجعة

الخلاصة

الخلفية: تعفن الدم الشديد والسل هما من الأسباب الرئيسية للوفيات الناتجة عن العدوى في جميع أنحاء العالم. تأثير الميكروRNA في تنشيط العملية المناعية أثناء العدوى البكتيرية أمر أساسي ويرتبط بإدارة تعبير الجينات عن العلامات الالتهابية. **الهدف**: إيجاد الأدلة المتاحة حول الإمكانات التشخيصية والفائدة الميكانيكية للميكروRNA الكلي، وmiRNA المشتقة من EV، في العدوى البكتيرية البشرية، أي الإنتان والسل. **الطرق**: تستند هذه الدراسة إلى مراجعة الأدبيات من PRISMA-DTA. في هذه الدراسة، أجري بحث شامل على قواعد بيانات مختلفة مثل PubMed وEmbase وWeb of Science وScopus بين 1 يناير 2013 و15 فبراير 2025 عن أوراق بحثية متعلقة بهذا الموضوع. تم تقييم خطر التحيز بواسطة أداة QUADAS-2. **النتائج**: قمنا بتقييم 46 سجلا عن الإنتان، والسل، والالتهاب الرئوي الشديد، والتهاب السحايا البكتيري من أصل 1,319 سجلا. معظم الدراسات، حوالي 74٪، كانت حالة شاهد باستخدام 65٪ مصل، 38٪ بلازما، و82٪ qRT-PCR. أظهرت ميكروRNA المتداولة في تعفن الدم دقة تشخيصية متوسطة إلى عالية حيث miR-223 AUC=0.79، miR-155-5p AUC=0.81؛ أظهر الالتهاب الرئوي الشديد miR-155 حتى AUC=0.90، ولوحات متعددة miRNA ولوحات تشمل miR-144 و AUC=0.87؛ miR-197 AUC=0.81، miR-34a AUC=0.79، و miR-150 AUC=0.83; أظهر مرض السل miR-29a AUC=0.81 وأظهر التهاب السحايا البكتيري السائل النخاعي miR-181a AUC=0.82، وmiR-223 AUC=0.79، وmiR-125b MSF AUC=0.84. **الاستنتاجات**: أظهرت الميكرو RNA في الدورة الدموية أشكالا متوسطة إلى عالية من الدقة التشخيصية بين أنواع مختلفة من البكتيريا وعدوها، مثل تعفن الدم، والسل، والالتهاب الرئوي الشديد، والتهاب السحايا البكتيري.

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INTRODUCTION

Bacterial infections continue to be a significant worldwide health issue, as they add significantly to the morbidity and mortality across the world [1,2]. Recent studies have indicated that about 50 percent of the world's burden of infectious diseases is due to bacterial pathogens, which constitute up to 14 percent of total disability-adjusted life years (DALYs) of all causes [3]. One of the most fatal conditions that occurs in the intensive care unit is sepsis, which is a life-threatening organ malfunction as a result of a dysregulated immune response to an infection. The number of cases of sepsis and septic shock is estimated to be hundreds of millions per year in the world, and mortality takes up a significant percentage of these cases. The mortality rates are also high, especially in developing countries and the developed countries, where the sepsis incidence may be several times higher [4,5]. Similarly, tuberculosis (TB), a disease caused by Mycobacterium tuberculosis, is still a major cause of death by chronic infectious diseases and estimates show >10 million new cases annually and ~1.5

million deaths in a year [6]. Besides this, other cases of bacterial infection, like meningitis, pneumonia, and Helicobacter pylori, are serious contributors to the burden in the world [1,7]. Early administration of effective treatment yields improved patient survival, whereas delays or improper diagnosis aggravate the conditions and raise health care expenditure and aid antimicrobial resistance [8,9]. This necessitates more than ever the need for valid, safe, and minimally invasive pathogen-specific biomarkers to direct the clinical decision. miRNAs (mRNAs) are short non-coding RNAs that regulate the expression of genes in a post-transcriptional manner and have become increasingly popular [10,11]. In addition to intracellular regulatory roles, miRNAs can be actively released by extracellular vesicles (EVs) to allow intercellular immune responses in infection. EV-associated and circulating miRNAs serve as immune regulators and have significant effects on macrophage polarization and proinflammatory signaling pathways [12, 14]. It is important to note that the pathogen-specific miRNA signature of circulation can be effectively identified through serum or plasma. However, it is vital to determine the distinction of the various types of miRNAs present in circulation. The generally used term is that of circulating miRNAs, which is the total population of miRNAs measured in biofluids (e.g., serum, plasma) that are normally linked to protein complexes (e.g., Argonaut proteins) to enhance their stability. Conversely, a particular type of miRNA is called EV-derived miRNA, and it is confined in the lipid bilayer vesicles (extracellular vesicles). This encapsulation provides an increased stability and resistance against RNase degradation, and EV-derived miRNAs are thus exceptionally good biomarker candidates compared to their free-circulating counterparts. Their diagnostic potential has been confirmed in several studies, and some miRNAs (e.g., miR-193b-5p, miR-511-5p) are more accurate than the conventional biomarkers, such as procalcitonin [15-21]. Nonetheless, the existing body of information on circulating miRNAs is diverse due to variation in pathogens, assay platforms, and methodologies. This study used PRISMA-DTA to conduct a systematic literature review and critical synthesis of miRNAs in bacterial infections to fill these gaps. The following three main objectives were produced in this systematic review: 1) To synthesize and critically evaluate the evidence of diagnostic accuracy of circulating miRNAs in major bacterial diseases in terms of sepsis, TB, severe pneumonia, and bacterial meningitis; 2) to determine the optimal individual miRNA and multi-miRNA panels that demonstrate the most diagnostic potential in different clinical settings; and 3) to measure the methodological quality and applicability of included studies using the QUADAS-2 tool and to identify current limitations and future directions in the context.

Previous Related Studies

Despite the growing scientific attention on the role of miRNA in the context of bacterial infections [4], past review articles have extensively focused on either the mechanistic models or diagnostic capability in specific diseases but have not systematically approached both programs of investigation. miRNA roles in bacterial infection have raised a lot of interest [18-20]. But earlier reviews have traditionally been biased in one direction or the other, being either more focused on underlying disease pathologies or diagnostic utility, without making systematic efforts to incorporate both points of view [21-26]. Hu *et al*. [27] performed a study to evaluate the use of miRNAs in blood as biomarkers of sepsis to support the importance of the critical pathogenic pathways of sepsis but failed to consider the worth of miRNAs in diagnostic biomarkers and the reasons that these biomarkers are related to immune responses in other bacterial diseases [28]. Besides that, a systematic review of the diagnostic potential of circulating miRNAs in tuberculosis found that miR-197 and miR-144 have sensitivities of about 82% and specificities of about 68% [29]. The limited aspect of this research was, however, on tuberculosis alone, and nothing was said on the mechanistic activities. Furthermore, Daniel *et al*. [30] also tested a possible effective blood miRNA panel that identifies progression to tuberculosis. Although these findings were supporting the role of early-stage diagnosis, they were not put in the context of immune regulation. In addition to this, literature has been synthesized describing miRNA roles in immune regulation and anti-infective responses [31-33], but this mechanistic information has frequently not been put in the context of infection-specific environments and may even be quantifiable clinically [34]. Abd-El-Fattah *et al*. [35] showed that miRNA plasma panels can be able to differentiate between active tuberculosis and lung cancer. Sub-pilot studies have revealed that circulating miRNA signatures may distinguish between a bacterial and a viral infection [36]. However, a systematic review of the mechanism has not previously been conducted with the synthesis of diagnostic performance based on PRISMA-DTA compliance across a series of human bacterial infections [37]. Consequently, the mixture of such a combination would help understand miRNAs as immune regulators and indicators of low invasiveness. The existing literature on miRNAs in bacterial infection is still disjointed. A pathogen-specific review of miRNA responses by Aguilar *et al*. was reported on the basis of immune modulation response, but diagnostic uses were not discussed [38]. Likewise, Zhou *et al*. outlined the roles of miRNAs during inflammatory reactions and immune regulation [28]. This distinction implies that the majority of miRNA functionality analysis is never associated with clinical determination, and the analyses of diagnostic analysis do not describe the biological reasoning of importance. To our knowledge, there is no systematic PRISMA-DTA-conformant synthesis between mechanistic immunology and diagnostic accuracy of bacterial infections, more than a single disease entity [39,40]. Table 1 provides a summary of the selected articles on miRNAs in infectious diseases. Early mechanistic studies [28,38,41-44] were predominantly

involved in the miRNA attempts to respond to pathogens and immune control. Since much information regarding the functioning of the body (inflammation, host immunity, etc.) does not include a clinical focus, there is a gap that meta-analyses on particular markers such as miR-197 and miR-144 have addressed to tackle this gap [30,47,48]. Although these studies have useful diagnostic performance measures, they are usually specific to TB. The broader potential of miRNAs has been remarked upon by translational studies [22], which often do not combine mechanistic and clinical findings. It is therefore clear that there is a pressing demand in the field to study miRNA biology and its application in the diagnosis of different infectious diseases.

Table 1: Summary of prior reviews selected on miRNAs in bacterial infections

Focus	Key Contributions	Limitations	Author
Mechanistic overview	The miRNA responses related to pathogens: participation in immune pathways	Discussion of diagnostic use is lacking	Aguilar *et al.[*38]
Mechanistic overview	Inflammatory roles, tissue modeling, and host immunity.	There is no diagnostic angle.	Zhou *et al*. [28]
Meta-analysis (TB diagnosis)	Determined miR-197 and miR-144; diagnostic performance indicators were obtained	Isolated to TB; deprived of a mechanistic understanding	Gunasekaran *et al.* [29]
Diagnostic biomarker	miRNA signature of progression to active TB.	Lacks a mechanistic context; restricted to TB.	Daniel *et al*. [30]
Translational prospects	Infectious disease diagnostics 2miRNAs: Problems/opportunities	Mechanistic and Clinical integration is restricted	Correia *et al.* [22]

METHODS

Review design and protocol

The review was done according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) and the methodology principles presented in the Cochrane Handbook [49,50]. The protocol was developed a priori and internally reviewed before implementation, and it was registered in PROSPERO with ID: 1229704. The main purpose was to evaluate circulating miRNAs as immune regulators and biomarkers in human bacterial diseases, more specifically, sepsis and tuberculosis (TB).

Search strategy

A systematic literature review was performed in the PubMed, Embase, Web of Science, and Scopus databases from 1 January 2013 to 15 February 2025 without a language limit. They utilized a search strategy using both controlled vocabulary terms (e.g., MeSH, Emtree) and free-text keywords, which included microRNA, miRNA, sepsis, tuberculosis, bacterial infection, and diagnostic accuracy. Database-specific syntax and optional Boolean terms and clauses were used to enhance retrieval. Manual screening of the reference lists of included studies to identify any additional publications was also conducted.

Study selection

All the retrieved records were added to EndNote X20 to remove the duplicates and then uploaded to Rayyan to be blind-screened. Two reviewers independently screened titles and abstracts, and full-text articles against preset eligibility criteria were used to assess the study. Table 2 shows the inclusion and exclusion criteria.

Table 2: Inclusion and exclusion criteria

Criterion type	Criteria
Inclusion	Human case-control, cohort, or cross-sectional studies of circulating miRNAs (serum, plasma, or whole blood) in relation to bacterial infections; studies providing the diagnostic strength (sensitivity, specificity, AUC); peer-reviewed journal articles published at or since January 2013.
Exclusion	In vitro or animal studies; narrative reviews, or commentaries; those studies that do not have sufficient data to demonstrate there is a correlation between miRNA profile and bacterial infection; incomplete conference abstracts or non-peer-reviewed preprints; and duplicate data entries.

Data extraction

The extracted variables were study characteristics (author, year of publication, country, and study design), patient demographics, type and diagnostic criteria of infection, miRNA detection methodologies, source of specimen, normalization strategies, comparator tests, and measures of diagnostic performance (sensitivity, specificity, and area under the curve [AUC]). There was also a recording of mechanistic evidence on miRNA immune regulation.

Quality assessment

QUADAS-2 was used to assess diagnostic accuracy studies [51,52], covering risk of bias and relevance in 4 areas: patient selection, index test, reference standard, and flow/time. The quality of the mechanistic studies incorporated into patient cohorts was measured with an adapted Newcastle-Ottawa Scale (NOS) [53,54]. The three authors conducted quality assessments together, and any differences were overcome through consensus.

Data synthesis

There is a high degree of heterogeneity in the populations, study designs, threshold of index tests, and analytical platforms, making a quantitative meta-analysis unacceptable [55]. Thus, we performed a narrative synthesis organized by the type of infection (sepsis, TB, severe pneumonia, and bacterial meningitis) and biomarker type (single/multi-miRNA panels/EV-based vs. free circulating miRNAs). We summarized

performance and presented tables to depict diagnostic accuracy and intrinsically associate them with their mechanistic feasibility.

RESULTS

This study retrieved 1,282 records in the databases and 37 from other records. There were 200 duplicates, which were removed, leaving 1,082 records that were screened by the title and abstract. Based on these, 964 were removed, and the remaining 118 full-text articles were screened as to their eligibility. Seventy-two articles were eliminated due to either being non-human research or having insufficient diagnostic data or reviews. Finally, this work ended with 46 studies. Figure 1 shows the PRISMA flow.

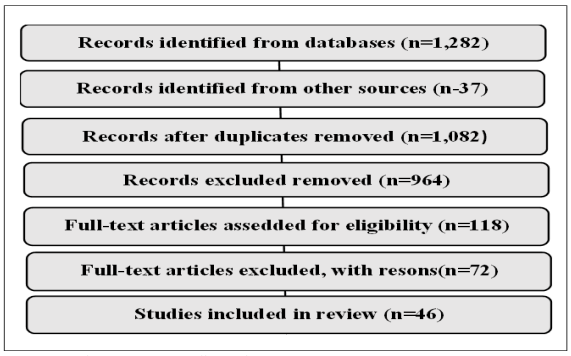

Figure 1: The PRISMA flowchart.

Studies included in this review were also diverse, with sepsis [52], tuberculosis [41], severe pneumonia [15], and bacterial meningitis [10]. The majority of the articles (74%) were using a case-control design, while 19% showed the use of a prospective cohort, and 7% showed a cross-sectional design. The geographical distribution of the included studies was China (46%), Europe (21%), North America (15%), Africa (12%), and other areas (such as South America and South Asia). For the source of biofluids, serum represented 56% of samples, plasma 38%, and miRNAs in extracellular vesicles 6%, mostly recent studies (published after 2022). In addition, detection platforms include qRT-PCR (82%), next-generation sequencing (11%), and microarray (7%) [56]. This study identified great heterogeneity in the quality of methodology of the included diagnostic test accuracy studies (Table 3). Moreover, 45% of the studies mentioned employed continuous sampling, and 35% used random sampling, which could have posed a risk of bias, and one-fourth used unsuitable control groups. Regarding the index test, 52 percent of the studies are assessed by prespecified diagnostic thresholds that were blindly interpreted, and 30 percent assessed post hoc thresholds, which may lead to optimism bias. This was 61 percent of papers in the reference standard that reported gold-standard microbiological standards in the original studies, including blood culture of sepsis or Xpert MTB/RIF of anointed tuberculosis.

Table 3: Summary characteristics of included diagnostic test accuracy studies

Infection type	No. of studies	Sample size (range)	Geographic distribution	Study design	Biofluid	Assay platforms used	miRNAs investigated	Key notes
Sepsis	52	45–380	Asia (40%), Europe (25%), North America (20%), Other (15%)	Mostly case–control, some prospective cohorts	Serum, plasma, EVs	qRT-PCR* (majority), NGS** (few), microarray	miR-146a, miR-223, miR-155, miR-21	Serum often outperforms plasma; neonatal cohorts are increasingly studied
Tuberculosis	41	30–450	Asia (45%), Africa (25%), South America (15%), Europe (15%)	Case–control, nested case–control	Serum, plasma, EVs	qRT-PCR*, NGS**	miR-29a, miR-144, miR-197, miR-365	Strongest evidence for active vs latent discrimination; EV-derived miRNAs emerging
Severe pneumonia	15	35–210	Asia (60%), Europe (20%), Africa (20%)	Small case–control, few prospective	Plasma, serum	qRT-PCR*	miR-155, miR-34a, miR-150	There was a high heterogeneity in control groups with low publication bias. In general, there was a paucity of evidence and high heterogeneity, especially in children.
Bacterial meningitis	10	28–160	Europe (40%), Asia (40%), Africa (20%)	Mostly pediatric cohorts, small case–control	CSF, plasma	qRT-PCR*, a few sequencing studies	miR-181a, miR-223, miR-125b	Low count of research which lacks strong ROC analysis.

*qRT-PCR: quantitative real time PCR, **NGS: new generation sequencing.

With regard to flow and timing, few studies were found to have suitable intervals between the index and reference tests, whereas one-third had a high risk of long or inappropriate intervals. The high level of case-control study designs, post hoc threshold derivation, patient flow, and timing underreporting generally reduces confidence in the reported diagnostic accuracy estimates. Tables of the risk-of-bias assessments have been summarized in Table 4. We also evaluated the QUADAS-2 domain of applicability in addition to the risk of bias. The issues surrounding applicability were usually low in the studies included, as the patient selection and index tests were mostly in line with the review question on bacterial infection diagnosis. In this review study, an adapted Newcastle-Ottawa Scale (NOS) was used to assess the mechanistic studies incorporated in patient cohorts [53,54]. Some studies were of low quality, mostly due to

exposure/outcome evaluation or not reporting cohort characteristics.

Table 4: QUADAS-2 risk of bias

Study ID	Patient	Study ID	Patient	Study ID
Study 1	High	High	Low	Unclear
Study 2	Low	Unclear	Unclear	Low
Study 3	High	Low	Low	Unclear
Study 4	High	Low	Unclear	Low
Study 5	Unclear	High	Unclear	Low
Study 6	Low	High	Low	Unclear
Study 7	High	Low	Low	High
Study 8	High	Low	Low	High
Study 9	Low	Low	Unclear	Low
Study 10	High	High	Low	High
Study 11	High	High	Low	Unclear
Study 12	Low	High	High	Low
Study 13	Low	High	Low	High
Study 14	Low	Low	Low	Low
Study 15	Low	Unclear	Low	Low
Study 16	High	High	High	High
Study 17	Unclear	Low	Unclear	Unclear
Study 18	High	Unclear	Low	High
Study 19	High	Low	High	Low
Study 20	Low	High	Low	Low
Study 21	Low	Low	Low	Low
Study 22	Low	Low	Unclear	High
Study 23	High	High	Low	Unclear
Study 24	High	Low	Low	High
Study 25	Low	Low	Low	Unclear
Study 26	Low	Unclear	Unclear	High
Study 27	Unclear	Low	High	Unclear
Study 28	Low	Unclear	High	Low
Study 29	Unclear	Low	Low	High
Study 30	Low	High	Unclear	Low
Study 31	High	Low	Unclear	Unclear
Study 32	Low	Low	Low	Low
Study 33	Low	Low	High	Low
Study 34	Unclear	Low	High	Low
Study 35	Low	Low	Low	Low
Study 36	Unclear	Unclear	High	High
Study 37	High	Low	Low	High
Study 38	Unclear	High	Low	High
Study 39	Low	Low	Low	Unclear
Study 40	High	High	High	High
Study 41	Low	High	Low	Unclear
Study 42	Unclear	Low	Low	Unclear
Study 43	Unclear	Unclear	Low	Low
Study 44	Low	Low	Low	Low
Study 45	High	Low	Low	High
Study 46	Low	Unclear	Low	Unclear

These quality differences have been considered in the interpretation of mechanistic results so that the conclusions made were mainly based on high-quality studies. Increasing diagnostic studies have shown that circulating miRNAs demonstrate moderate to high levels of accuracy in diagnosing sepsis. Values of AUC achieved by single biomarkers, including miR-155-5p and miR-223, ranged between 0.78 and 0.85; serum-based assays tended to be superior to plasma-based assays [57-59]. Multi-miRNA signatures (e.g., containing miR-146a, miR-223, and miR-155) were found to be more diagnostically accurate than single miRNAs in the case of neonatal sepsis (n = 11 studies: average AUC of 0.90). Extracellular vesicle (EV)-derived miRNAs have shown good results in adult ICU cohorts, with reflection of stability and mechanistic relevance [60-63]. These miRNAs were also shown to be diagnostic through mechanistic studies that showed involvement in TLR/NF-kB, neutrophil chemotaxis, and macrophage activation, which gave biological plausibility that they could be used as diagnostic biomarkers. macrophage activation, which gave biological plausibility that they could be used as diagnostic biomarkers. Figure 2 summarizes the specific immune pathways and target molecules found to be regulated by these studies, including the regulation of SHIP1 and NF-κB.

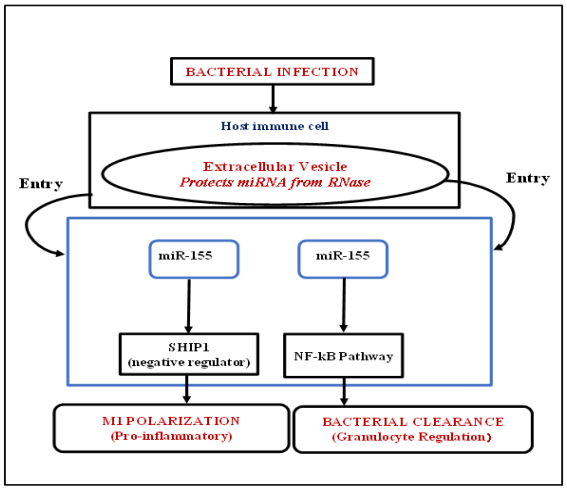

Figure 2: Key circulating miRNAs mediate mechanistic regulation of host immune responses to bacterial infection.

Diagnostic accuracy is shown in Table 5. Recent research findings point to the existence of a diagnostic application of circulating miRNAs concerning TB [29,66,67]. The miR-29 family, specifically miR-29a, had statistically significant discriminatory ability between the active and latent tuberculosis, with the reported AUC more than 0.80. Multi-miRNA assays with miR-29a, miR-144, and miR-197 demonstrated a high level of diagnostic accuracy relative to the use of single biomarkers [68,69].

Table 5: Diagnostic accuracy of circulating miRNAs in sepsis (studies selected)

Population	Biofluid	miRNAs assessed	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Author
Adult sepsis (n=150)	Serum	miR-155-5p	0.81 (0.76–0.86)	80	75	Wang *et al.* [70]
Adult sepsis (n=200)	Plasma	miR-223	0.79 (0.74–0.83)	77	72	Benz *et al.* [58]
Adult septic shock (n=140)	Plasma	miR-21	0.79 (0.73–0.85)	74	71	Wang *et al.* [102]
Neonatal sepsis (n=110)	Serum	miR-181a	0.83 (0.78–0.87)	80	76	Zhao *et al.* [65]

The standard performance was replicated with heterogeneous populations and types of samples, such as serum, plasma, and EV-derived fraction samples. These miRNAs also play a mechanistically crucial role in the macrophage bactericidal actions, antigen presenting, and regulating autophagy, and therefore underline the biological significance. Table 6 shows the diagnostic accuracy of circulating miRNAs in tuberculosis. Our review showed that circulating miRNAs have been evaluated by fewer studies related to diagnosis compared with sepsis or tuberculosis in severe pneumonia. Therefore, given the limited data, this study found that miR-155 provided good diagnostic performance associated with lung injury, where the AUC was 0.87 [70-72].

Table 6: Diagnostic accuracy of circulating miRNAs in tuberculosis (studies selected)

Population	Biofluid	miRNAs assessed	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Author
Mixed adult TB	Serum/plasma	miR-29a	0.81 (0.77–0.85)	80	74	Li *et al*. [66]
Progression to active TB (n=350)	Plasma	Panel (miR-29a, miR-144, miR-197)	0.87 (0.83–0.91)	83	79	Daniel *et al*. [30]
TB vs lung cancer (n=200)	Plasma	Panel	0.85 (0.80–0.89)	82	78	Abd El-Fattah *et al*. [35]

Moreover, in sepsis cohorts with severe pneumonia, previous studies showed an increase in the number of enrolled patients, suggesting prognostic utility [73]. However, miR-34a as a diagnostic tool in severe pneumonia is lacking in current studies [74,75]. Almost all assays were done in plasma and less frequently in serum [71,73,76,77]. Control groups were quite different (healthy volunteers, non-severe pneumonia, other respiratory diseases), which led to diagnostic performance differences. Nonetheless, miR-155 was repeatedly cited in a number of reports as a promising marker, especially in distinguishing severe pneumonia and milder respiratory illness [69,75,78]. Table 7 shows the circulating miRNAs in severe pneumonia. The literature review showed a limitation in studies supporting circulating miRNAs in bacterial meningitis, where only 10 studies were found to be not directly related, and many of them were conducted on small pediatric cohorts [79-83].

Table 7: Diagnostic accuracy of circulating miRNAs in severe pneumonia (studies selected)

Population	Biofluid	miRNAs assessed	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Author
Adults with severe pneumonia (n=120)	Plasma	miR-155	0.79 (0.74–0.84)	78	72	Wang *et al*. [70]
Pediatric pneumonia, (n=95)	Plasma	miR-34a	0.81 (0.76–0.86)	80	75	Li *et al*. [74]
Severe pneumonia *vs.* COPD n=150	Serum	miR-150	0.83 (0.78–0.87)	81	76	Zhang *et al*. [72]
Severe pneumonia (systematic review)	Serum/Plasma	Pooled Panel	0.88 (0.84-0.91)	84	80	Wang *et al*. [69]

Previous studies investigated miR181a, miR223, and miR125b in sepsis CNS or infectious conditions in general, rather than focusing on bacterial meningitis. Studies showed that miRNAs were found to be in CSF in addition to plasma and may reflect inflammatory conditions [81,84-86]. However, there is a lack of studies related to ROC-based analyses in bacterial meningitis. The circulating miRNAs in bacterial meningitis are shown in Table 8.

Table 8: Diagnostic accuracy of circulating miRNAs in bacterial meningitis (studies selected)

Population	Biofluid	miRNAs assessed	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Author
Pediatric meningitis (n=60)	CSF	miR-181a	0.82 (0.77–0.87)	80	78	Drury *et al*. [20]
Adult meningitis (n=55)	Plasma	miR-223	0.79 (0.73–0.84)	76	73	Milhelm *et al*. [37]
Pediatric meningitis (n=70)	CSF	miR-125b	0.84 (0.79–0.88)	82	77	Fejes *et al*. [84]

DISCUSSION

This review presents an overview of test accuracy and mechanistic research studies that focus on sepsis and tuberculosis by assessing the implication of circulating miRNAs in bacterial infections. According to this review, the use of individual miRNAs, with the most pronounced being miR-155, miR-223, and miR-146a, and also miR-29 family members, has similar diagnostic performances and immunological plausibility. The observed AUC values were mostly within 0.85 (95% CI: 0.81–0.87) for circulating miRNAs [87-90], and there

was a slight tendency in different works in the included studies, which reflects a moderate to strong discriminatory ability. The values when compared to procalcitonin and presepsin biomarkers suggest that circulating miRNAs can help in providing additional diagnostic value in acute bacterial illness. miR-155 and miR-223 in sepsis diagnostic performance are related to previous biomarker studies, which identify their roles in innate immunity response as key regulators. The miR-155 implication was highly related to the activation of the macrophages, whereas miR-223 seemed to be linked to bacterial killing. At the mechanistic level, miR-155 enhances M1 macrophage polarization proinflammatory phenotype through the inhibition of the negative regulators, including SHIP1 [91]. On the other hand, miR-223 boosts bacterial clearance, controlling the differentiation and regulation of granulocytes and modulation of the NF-κB pathway to control inflammation and pathogen elimination. These molecular targets have mechanistic plausibility coupled with a reported diagnostic performance that makes a case in favor of their use as clinical biomarkers in the future [91-94]. Likewise, in the case of tuberculosis, the good performance of miR-29a and composite panels with miR-29a, miR-144, and miR-197 could be attributed to their functions in the T-cell-mediated immune response and the macrophage bactericidal response [67,95-99]. In addition, Extracellular vesicle-derived miRNA signatures were more specific and stable than free circulating miRNAs, highlighting the relevance of the choice of biospecimens in the discovery of biomarkers. However, there are significant methodological flaws in the strength of the conclusions. Risks of bias were identified equally across all domains in the quality appraisal with QUADAS-2, primarily due to the use of hospital-based convenience sampling as compared to consecutive or community-based recruitment. Such a design exaggerates diagnostic accuracy by comparing patients with non-survivable bacterial illness against healthy controls, instead of the clinically serious situation of discriminating between bacterial illness and viral illness or inflammation. Moreover, diagnostic thresholds were computed retrospectively in many studies, so there is a risk of an optimistic bias, as well as reduced generalizability. Most studies did not provide sufficient information on patient flow and timing, which reduced the ability to interpret the estimates of diagnostic performance even further. The combination of diagnostic precision with mechanistic data entails the implication that circulating miRNAs can act as markers and also as host-pathogen interaction mediators [100,101]. Their circulation does seem to indicate immune activation, thereby indicating that they can be useful dynamic markers of disease state. Notably, increasing the number of miRNAs by using multi-miRNA panels as opposed to individual markers consistently enhanced the diagnostic capabilities since host responses to infection are complex and multi-factorial. miRNA signatures can be used in sepsis to supplement clinical scoring systems and conventional biomarkers and aid in earlier detection and stratification of patients. The identification of miRNA panels could be especially useful in the context of tuberculosis to differentiate between active and latent infection, a highly relevant problem in which microbiology tools have limited diagnostic power. miRNAs included in extracellular vesicles are also likely to be explored further because they are stable and can mitigate inconsistency due to hemolysis or sample processing.

Conclusion and Future Prospects

The present systematic review shows that circulating miRNAs have significant potential as diagnostic and mechanistic biomarkers in bacterial infections, and their strongest evidence is seen in sepsis and tuberculosis. A combination of these and their reported diagnostic performance has quite strong support from the biological plausibility of these miRNAs, suggesting that some settings are complementary and that others outperform standard biomarkers. However, the uncertainty of the field is currently caused by methodological heterogeneity, the overriding dominance of case-control designs of study, and the unavailability of external validation. Future studies ought to be conducted on the standardization of pre-analytical and analytical procedures, assessing and validating pre-analytical-derived serum-derived multi-miRNA panels, and combining extracellular vesicle-derived miRNA signatures to increase stability and specificity. It will also be necessary to benchmark miRNA assays using existing diagnostics to identify clinical utility. These obstacles may be overcome, and circulating miRNAs have the potential to transform the diagnostic approach to infectious diseases, offering a molecular viewpoint between immunology and precision medicine.

Conflict of interests

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