

Diagnostic Value of MicroRNAs as Biomarkers for Sepsis-associated Acute Kidney Injury: A Systematic Review and Meta-Analysis

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Introduction. Sepsis-associated acute kidney injury (SA-AKI) is a common and serious complication in critically ill patients, associated with high morbidity and mortality. Early diagnosis remains challenging due to the limitations of traditional biomarkers such as serum creatinine and urine output. MicroRNAs (miRNAs) and circular RNAs (circRNAs) have emerged as promising non-invasive biomarkers for early SA-AKI detection. To systematically evaluate the diagnostic accuracy of individual non-coding RNA biomarkers for predicting SA-AKI in sepsis patients.

Methods. We systematically searched PubMed from inception to August 2026 and manually screened reference lists of relevant systematic reviews. Studies were included if they evaluated non-coding RNAs for SA-AKI diagnosis in sepsis patients, compared sepsis patients with AKI to sepsis patients without AKI.

Results. Fourteen studies comprising 1,840 patients (908 with SA-AKI and 932 controls) were included. The pooled sensitivity was 83.5% and pooled specificity was 81.5%. The pooled DOR was 22.29, and the area under the HSROC curve was 0.885, indicating excellent diagnostic accuracy. The most promising individual biomarkers identified were miR-210 (AUC = 0.913), miR-155 (AUC = 0.910), miR-132-3p (AUC = 0.910), and miR-769-5p (AUC = 0.928). Heterogeneity was low to moderate (I^2 : 30.4 to 35.9% for sensitivity, 0.8 to 0.9% for specificity).

Conclusions. Individual non-coding RNA biomarkers demonstrate good to excellent diagnostic accuracy for SA-AKI, with performance comparable to or exceeding that of established protein biomarkers. Their biological plausibility, stability in body fluids, and potential for early detection make them attractive candidates for clinical translation.

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INTRODUCTION

Sepsis is one of the greatest critical care challenges and is estimated to cause 11 million deaths globally every year, consuming a significant amount of intensive care resources. Despite improvements in early recognition and treatment, mortality in

septic patients has been reported as between 20 and 50%, depending on the severity of the disease.^{1,2}



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Sepsis can have a multitude of complications, and acute kidney injury (AKI) is one of the most frequent, occurring in 20 to 50% of septic patients and representing a distinct and independent poor prognostic factor.³⁻⁵ This systemic inflammatory process, combined with microvascular dysfunction, oxidative stress, mitochondrial injury, and tubular epithelial cell damage, is a multifactorial phenomenon and not merely a reflection of poor renal perfusion; it constitutes sepsis-associated AKI (SA-AKI).⁶

Early diagnosis of SA-AKI remains challenging. The current clinical standard, serum creatinine, only increases after significant nephron loss and is influenced by non-renal factors including muscle mass, hydration status, and medication use.^{7,8} Protein-based biomarkers that have attempted to fill this void have yielded only moderate and inconsistent diagnostic value in studies, with AUCs of 0.65 to 0.87 reported in most studies.⁹⁻¹²

MicroRNAs (miRNAs) are emerging as potential biomarkers for SA-AKI. These small non-coding RNAs are released into circulation and urine in tissue- and injury-specific patterns, and their release into plasma is linked to key pathophysiological pathways involved in sepsis-induced renal injury, such as hypoxic signaling and inflammatory cascades.¹³⁻¹⁸ Importantly, miRNAs are highly resistant to RNase degradation, withstand repeated freeze-thaw cycles, and are clinically stable in body fluids, making them promising candidates for clinical assays.¹⁹ In addition to miRNAs, circular RNAs (circRNAs) have recently emerged as potential biomarkers. These covalently closed non-coding RNAs are remarkably stable due to their resistance to exonuclease degradation and have been shown to function as miRNA sponges, making them attractive diagnostic targets.²⁰⁻²² Several studies have focused on particular miRNAs, multi-marker miRNA panels, or circRNAs as diagnostic markers for SA-AKI. However, these studies have generally been small and heterogeneous. Previous reviews in this field have been narrative or have not quantitatively synthesized diagnostic accuracy data comparing individual non-coding RNA biomarkers.²³⁻²⁶

The aim of this systematic review and meta-analysis was to quantify the diagnostic accuracy

of individual non-coding RNA biomarkers for the diagnosis of SA-AKI, and to evaluate their potential clinical utility compared to established protein-based biomarkers.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁷

Search Strategy

We systematically searched the PubMed database from inception to August 2026. Additionally, we manually screened the reference lists of four relevant systematic reviews²³⁻²⁶ to identify additional studies. The search strategy combined terms for microRNAs, sepsis, acute kidney injury, and diagnostic accuracy.

The following search strings were applied:

1. ("miR-210" OR "microRNA-210") AND ("sepsis" OR "septic") AND ("acute kidney injury" OR "AKI") AND ("diagnostic" OR "biomarker")
2. ("miR-582-5p" OR "microRNA-582-5p" OR "miR-23a-3p" OR "microRNA-23a-3p" OR "miR-320-3p" OR "microRNA-320-3p" OR "miR-22-3p" OR "microRNA-22-3p" OR "miR-15a-5p" OR "microRNA-15a-5p") AND ("sepsis" OR "septic") AND ("acute kidney injury" OR "AKI") AND ("diagnostic" OR "biomarker" OR "ROC" OR "AUC")
3. ("microRNAs"[MeSH Terms] OR "microRNA"[Title/Abstract] OR "miRNA"[Title/Abstract] OR "miR-"[Title/Abstract]) AND ("acute kidney injury"[MeSH Terms] OR "acute kidney injury"[Title/Abstract] OR "AKI"[Title/Abstract] OR "acute renal injury"[Title/Abstract]) AND ("sepsis"[MeSH Terms] OR "sepsis"[Title/Abstract] OR "septic"[Title/Abstract]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "Meta-Analysis"[Title/Abstract] OR "Systematic Review"[Title/Abstract])

Eligibility Criteria

Studies were included if they: 1) evaluated miRNAs, circRNAs, or other non-coding RNAs as diagnostic biomarkers for sepsis-associated acute

kidney injury (SA-AKI) in human populations; 2) reported diagnostic accuracy data including AUC, sensitivity, and specificity, or provided sufficient information to construct a 2×2 contingency table; 3) used validated AKI definitions based on KDIGO, AKIN, or RIFLE criteria; 4) compared sepsis patients with AKI to sepsis patients without AKI; and 5) were published in English.

We excluded: 1) preclinical or animal studies; 2) in vitro investigations without clinical validation; 3) review articles, editorials, conference abstracts, and case reports; 4) studies not specifically focused on sepsis-associated AKI; 5) studies comparing AKI patients to healthy controls without a sepsis-non-AKI group; 6) studies evaluating AKI of mixed etiologies not exclusively sepsis-related; 7) articles with incomplete diagnostic data; 8) retracted publications; and 9) studies with unavailable full text.

For Chinese-language studies identified during the search, we utilized DeepSeek (深度求索), an artificial intelligence language model, to translate the full texts into English and assist with data extraction. The translated content was independently verified by two reviewers to ensure accuracy and consistency of the extracted variables.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts (FJG and DG), followed by full-text assessment of potentially eligible articles. Disagreements were resolved through discussion or consultation with a third reviewer (L.L or IAD).

Data extraction was performed using a standardized form that captured:

- Study characteristics: author, year, country, and design
- Sample characteristics: sample type (serum, plasma, urine, or whole blood)
- AKI definition: KDIGO, AKIN, RIFLE, or other criteria
- Biomarker information: biomarker(s) evaluated, category (single miRNA, best-performing miRNA from multi-miRNA panel, or circRNA)
- Diagnostic accuracy metrics: AUC with 95% CI, sensitivity, specificity
- 2×2 contingency table data: true positives,

false positives, false negatives, and true negatives

- Sampling timing: early (within 24 hours of admission), at diagnosis (at the time of clinical diagnosis), or late (at renal replacement therapy initiation)
- Assay methodology: RNA extraction kit, normalization method, detection chemistry, PCR platform

For Chinese-language publications, data extraction was performed with the assistance of DeepSeek AI translation, followed by manual verification by the review team.

Quality Assessment

Methodological quality was evaluated using the QUADAS-2 tool, which assesses risk of bias across four domains: patient selection, index test, reference standard, and flow and timing.²⁸ Each domain was rated as low, high, or unclear risk of bias, and applicability concerns were also assessed for each domain.

Statistical Analysis

All meta-analyses were conducted using R software (version 4.5.2) with the metafor, meta, and mada packages.

The primary outcomes were pooled sensitivity, specificity, and diagnostic odds ratio (DOR). A bivariate random-effects model²⁹ was applied to account for between-study heterogeneity and the correlation between sensitivity and specificity. The hierarchical summary receiver operating characteristic (HSROC) model was used to generate the summary ROC curve and estimate the area under the curve (AUC).³⁰ To handle zero cells in 2×2 tables, a continuity correction of 0.5 was added to all cells.³¹ For one study (Fan *et al.*³²), the reported AUC was 1.91 (95% CI: 1.61 to 2.19), which is mathematically impossible. We inferred that this represented a reporting error and used the value 0.910, which is consistent with the reported sensitivity (91.12%) and specificity (84.52%).

Between-study heterogeneity was quantified using the I^2 statistic and Cochran's Q test. I^2 values below 25% indicated low heterogeneity, 25 to 50% moderate heterogeneity, and above 50% high heterogeneity.³³ For the bivariate model, I^2 was

calculated using Holling's approach (sample size unadjusted for sensitivity, sample size adjusted for specificity) and the Zhou and Dendukuri approach. Subgroup analyses were performed to explore potential sources of heterogeneity based on clinically relevant variables, including sampling time, sample type, and detection chemistry.³³

Publication bias was evaluated using Egger's regression test with sample size as the predictor,³⁴ Begg's rank correlation test,³⁵ visual inspection of funnel plots, and trim-and-fill analysis.³⁵ Egger's regression test was implemented using the regtest function in the metafor package with predictor = "ni" to model the relationship between study precision (sample size) and effect size on the logit scale. Trim-and-fill analysis was performed using the L0 estimator for sensitivity and the R0 estimator for specificity, following the default recommendations of the metafor package. All tests were two-sided with a significance level of $P < .05$. The complete, reproducible R script used for all analyses (data entry, bivariate random-effects modeling, subgroup analyses, miR-210 cross-study comparison, publication bias assessment, and funnel plot generation) is provided as Supplementary Code S1.

Study Selection

The systematic literature search identified 46 records from database searches and 280 additional records from the reference lists of four systematic reviews. After removing 4 duplicates, 322 records were screened by title and abstract, of which 270 were excluded. The remaining 52 full-text articles were assessed for eligibility. Of these, 14 studies (26.9%) provided complete diagnostic accuracy data (2×2 contingency tables, AUC, sensitivity, and specificity) comparing sepsis patients with AKI to sepsis patients without AKI and were included in the quantitative meta-analysis: 11 single miRNA marker studies, 1 study reporting an individual miRNA from a multi-miRNA panel (from which the best-performing miRNA was extracted), and 2 circRNA studies (Table 1).

Thirty-eight studies (73.1%) were excluded for the following reasons: incomplete diagnostic data (lack of sensitivity/specificity reporting or absence of 2×2 contingency tables); different study populations (e.g., neonatal sepsis, non-sepsis AKI); comparison

Table 1. Characteristics and Diagnostic Performance of Included Biomarkers for Sepsis-associated AKI

#	Study	Year	Country	Biomarker	Sample	Timing	AKI Definition	Total (AKI/Control)	AUC (95% CI)	Sens (%)	Spec (%)
1	Zhang et al. ³⁹	2026	China	miR-210	Serum	Early	KDIGO	81 (41/40)	0.913	92.21	91.37
2	Liu et al. ⁴⁰	2020	China	miR-452	Urine	At Dx	KDIGO	97 (47/50)	0.899	87.23	78.00
3	Susianti et al. ⁴¹	2024	Indonesia	miR-210 ^a	Serum	At Dx	KDIGO	52 (26/26)	0.777	84.60	63.90
4	Fan et al. ³²	2024	China	miR-155	Serum	Early	RIFLE	150 (79/71)	0.910b	91.12	84.52
5	Chen et al. ⁴²	2026	China	miR-4772-3p	Serum	At Dx	KDIGO	192 (93/99)	0.864	85.10	84.00
6	Peng et al. ⁴³	2025	China	miR-769-5p	Serum	Early	Not specified	162 (82/80)	0.928	87.80	83.80
7	Wang et al. ⁴⁴	2026	China	miR-379-5p	Serum	Early	KDIGO	159 (74/85)	0.820	75.70	72.90
8	Tian et al. ⁴⁵	2026	China	miR-151a-3p	Serum	Early	KDIGO	208 (110/98)	0.883	84.60	77.60
9	Gong et al. ⁴⁶	2024	China	miR-625-5p	Serum	Early	KDIGO	120 (62/58)	0.844	79.03	74.60
10	Wu S-Y et al. ⁴⁷	2020	China	miR-21-3p	Serum	Early	KDIGO	142 (49/93)	0.863	87.50	81.60
11	Lan et al. ⁴⁸	2026	China	miR-132-3p	Plasma	At Dx	KDIGO	208 (108/100)	0.910	82.40	91.00
12	Xu et al. ⁴⁹	2025	China	miR-577 ^b	Urine	Early	KDIGO	135 (70/65)	0.888	80.0	86.15
13	Pu et al. ²²	2026	China	hsa_circ_0056869	Plasma	Early	KDIGO	68 (34/34)	0.818	79.41	82.35
14	Peng et al. ²¹	2024	China	hsa_circ_0072463	Plasma	Early	KDIGO	66 (33/33)	0.866	78.8	87.9
Total									N = 1,840z		

Abbreviations: Dx, diagnosis; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, End-stage kidney disease; AUC, area under the receiver operating characteristic curve; CI, confidence interval; Sens, sensitivity; Spec, specificity.

^aSusianti et al. specifically measured the miR-210-3p strand; both miR-210 and miR-210-3p are grouped as miR-210 for pooling.

^bAUC corrected from the reported value of 1.91, which is mathematically impossible; 0.910 is consistent with the reported sensitivity and specificity.

groups other than sepsis-non-AKI (e.g., healthy controls, ATN vs. HRS); or reporting multi-marker panels without individual biomarker data. The PRISMA flow diagram is presented in Figure 1.

Study Characteristics

A total of 14 studies were included in the meta-

analysis. The studies were published between 2020 and 2026, with the majority ($n = 13$, 92.9%) published in 2020 or later, reflecting the growing interest in non-coding RNA biomarkers for SA-AKI. The included studies originated from 2 countries: China ($n = 13$, 92.9%) and Indonesia ($n = 1$, 7.1%). Of the 14 studies, 11 (78.6%) evaluated single

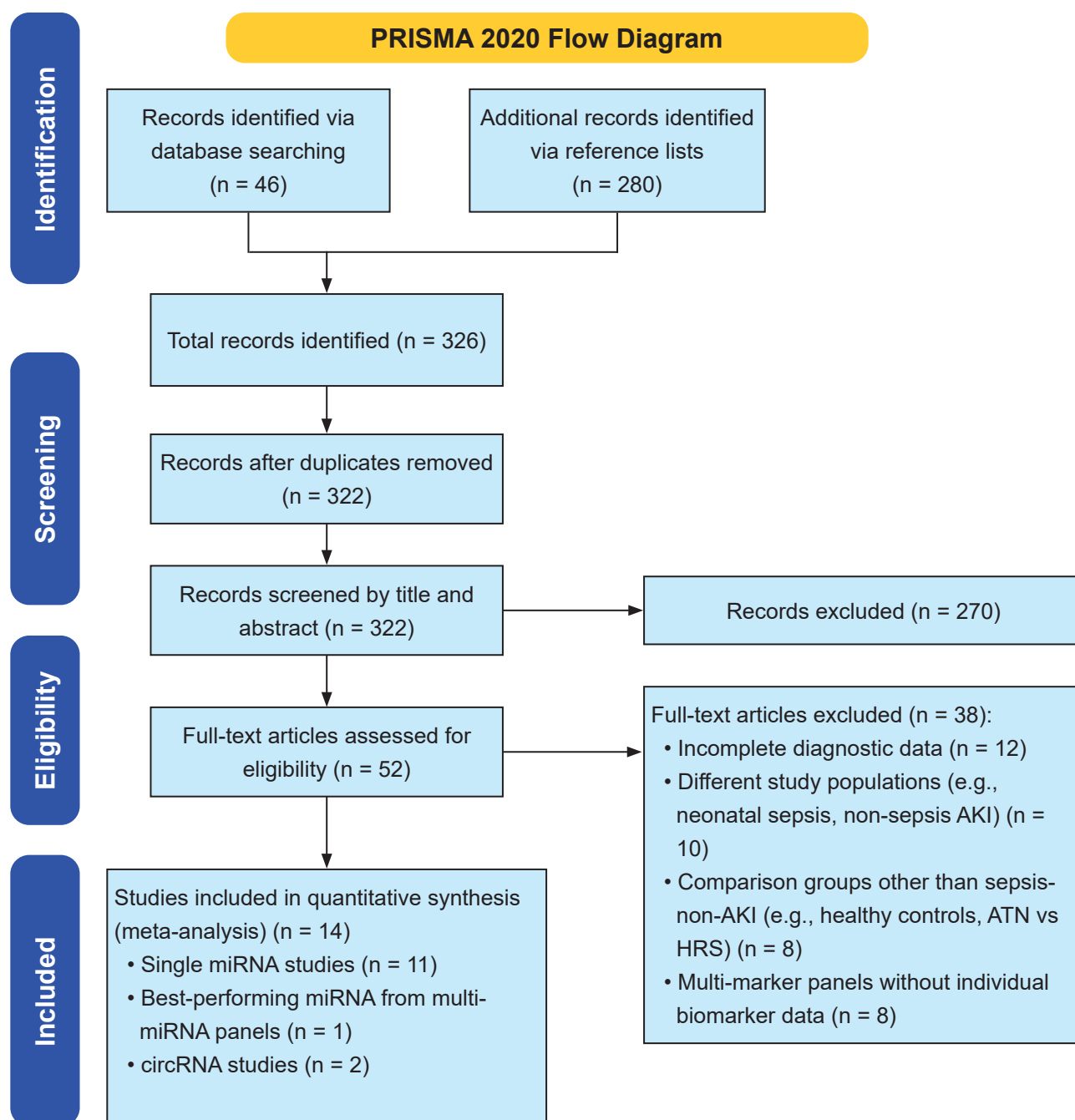


Figure 1. PRISMA Flow Diagram of Study Selection

Flow diagram showing the identification, screening, eligibility, and inclusion of studies for the systematic review and meta-analysis. A total of 322 records were screened, of which 52 full-text articles were assessed for eligibility, resulting in 14 studies included in the quantitative synthesis.

miRNA markers, 1 (7.1%) reported an individual miRNA from a multi-miRNA panel (from which the best-performing miRNA was extracted), and 2 (14.3%) evaluated circRNA biomarkers. Sample types included serum (n = 9, 64.3%), plasma (n = 3, 21.4%), and urine (n = 2, 14.3%). AKI was defined using KDIGO criteria (n = 12, 85.7%) or RIFLE criteria (n = 1, 7.1%); one study (7.1%) did not explicitly report the AKI diagnostic criteria used. The most commonly investigated biomarkers were miR-210 (n = 2, 14.3%), with all other biomarkers evaluated in single studies. The 2 × 2 contingency table data for all studies are presented in Table 2, and the detailed assay methods are summarized in Table 3. Regarding sepsis diagnostic criteria, 12 studies (85.7%) employed the Sepsis-3 definitions, while one study (Gong *et al.*) used the 2001 SCCM/ESICM/ACCP/ATS/SIS criteria, and one pediatric study (Wu *et al.*) used the Chinese Pediatric Sepsis Shock Expert Consensus (2015 version). Notably, Wu *et al.* was the only study including a pediatric population, with all other 13 studies conducted in adult populations.

The 14 included studies comprised 1,840 patients (908 with SA-AKI and 932 controls), with 11 single miRNA studies (n = 1,571 patients), 1 study with a best-performing miRNA from a panel (n = 135 patients), and 2 circRNA studies (n = 134 patients). The characteristics of all included studies are

summarized in Table 1.

The methodological quality of the 14 included studies was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool, which evaluates four domains: patient selection, index test, reference standard, and flow and timing. A summary of the quality assessment is presented in Figure 2.

Patient Selection: The majority of studies (n = 10, 71.4%) were at low risk of bias, as they included consecutive or random patient samples and avoided inappropriate exclusions. Four studies (28.6%) were at unclear risk due to insufficient reporting of sampling methods. No studies were at high risk of bias in this domain.

Index Test: All 14 studies (100%) were at low risk of bias for the index test domain, as they prespecified the miRNA / circRNA cut-off values or used standardized methods (RT-qPCR) for RNA quantification.

Reference Standard: Thirteen studies (92.9%) used validated AKI definitions (KDIGO or RIFLE criteria) and were at low risk of bias. One study (7.1%) did not explicitly report the AKI diagnostic criteria used and was classified as unclear risk of bias. No studies were at high risk of bias in this domain.

Flow and Timing: The majority of studies (n = 11, 78.6%) were at low risk of bias, as they

Table 2. Two-by-Two Contingency Tables Derived from Reported Diagnostic Accuracy

#	Study	Biomarker	Total (n)	TP	FP	FN	TN
1	Zhang <i>et al.</i> 2026	miR-210	81	38	4	3	36
2	Liu <i>et al.</i> 2020	miR-452	97	41	11	6	39
3	Susianti <i>et al.</i> 2024	miR-210 ^a	52	22	9	4	17
4	Fan <i>et al.</i> 2024	miR-155	150	72	11	7	60
5	Chen <i>et al.</i> 2026	miR-4772-3p	192	79	16	14	83
6	Peng <i>et al.</i> 2025	miR-769-5p	162	72	13	10	67
7	Wang <i>et al.</i> 2026	miR-379-5p	159	56	23	18	62
8	Tian <i>et al.</i> 2026	miR-151a-3p	208	93	22	17	76
9	Gong <i>et al.</i> 2024	miR-625-5p	120	49	15	13	43
10	Wu S-Y <i>et al.</i> 2020	miR-21-3p	142	43	17	6	76
11	Lan <i>et al.</i> 2026	miR-132-3p	208	89	9	19	91
12	Xu <i>et al.</i> 2025	miR-577	135	56	9	14	56
13	Pu <i>et al.</i> 2026	hsa_circ_0056869	68	27	6	7	28
14	Peng <i>et al.</i> 2024	hsa_circ_0072463	66	26	4	7	29
Total			1,840	763	169	145	763

Note. Cell counts (true positive [TP], false positive [FP], false negative [FN], true negative [TN]) were back-calculated from the reported total sample size and diagnostic accuracy metrics (sensitivity and specificity) for use in meta-analytic pooling. Non-integer values reflect rounding during back-calculation from reported sensitivity and specificity.

^aSusianti *et al.* specifically measured the miR-210-3p strand; Zhang *et al.* did not specify the strand. Both are referred to as miR-210 for pooling purposes.

Table 3. Sample Handling and Assay Methodology of Included Studies

#	Study	Sample Type	RNA Extraction Kit	Normalization Method	Detection Chemistry	PCR Platform	Assay Kit / Reagents
1	Zhang et al. 2026	Serum	miRNA test kit (Invitrogen)	Endogenous (U6 snRNA)	SYBR Green	Not specified	Reverse transcription kit (Fermentas)
2	Liu et al. 2020	Urine/Serum	mirVana; miRNeasy (Qiagen)	Exogenous (cel-miR-39); Endogenous (sno202)	TaqMan	Not specified	TaqMan MicroRNA RT Kit; TaqMan assay kit (Applied Biosystems)
3	Susianti et al. 2024	Serum	microRNA isolation kit (Tiangen)	Endogenous (hsa-U6)	SYBR Green	Not specified	qRT-PCR kit (Tiangen Biotech)
4	Fan et al. 2024	Serum	Not specified	Endogenous (U6)	SYBR Green	9700 gene amplification instrument	Primers synthesized by Invitrogen
5	Chen et al. 2026	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	LightCycler 480 (Roche)	Reverse transcription kit (Takara)
6	Peng et al. 2025	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	Not specified	miScript II RT Kit (Qiagen); SuperScript IV RT Kit (Invitrogen)
7	Wang et al. 2026	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	CFX real-time PCR (Bio-Rad)	PrimeScript RT kit (Takara); Mir-X miRNA synthesis kit (Takara)
8	Tian et al. 2026	Serum/Cells	TRIzol (Invitrogen); miRNeasy (Qiagen)	Endogenous (U6 for miRNA; GAPDH for mRNA)	SYBR Green	QuantStudio 5 (Applied Biosystems)	miRcURY LNA RT Kit (Qiagen); PrimeScript RT Kit (Takara)
9	Gong et al. 2024	Serum/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6)	SYBR Green	7500 Real-Time PCR (Applied Biosystems)	RT kit (Takara); IQ SYBR Green Supremix (Bio-Rad)
10	Wu S-Y et al. 2020	Serum	Rapid RNA Extraction Kit	Endogenous (U6)	TaqMan	ABI7500 Real-Time PCR (Applied Biosystems)	TaqMan MicroRNA Assay; TaqMan 2× Universal PCR Master Mix
11	Lan et al. 2026	Plasma/Cells	TRIzol (Invitrogen)	Not specified (GAPDH primers listed but not confirmed as internal control) ^a	—	—	—
12	Xu et al. 2025	Urine	Trizol kit (Dakwi Biotechnology)	Endogenous (U6)	SYBR Green	Not specified	Reverse transcription kit (Wanbo Biomedical)
13	Pu et al. 2026	Plasma/Cells	TRIzol reagent (Thermo Fisher)	Endogenous (U6 for miRNA; β-tubulin for mRNA)	SYBR Green	LightCycler 480 (Roche)	PrimeScript RT kit with gDNA Eraser (Takara); AG SYBR Green Pro Taq HS Premix
14	Peng et al. 2024	Plasma/Cells	TRIzol reagent (Invitrogen)	Endogenous (U6 for miRNA; β-tubulin for mRNA)	SYBR Green	LightCycler 480 (Roche)	PrimeScript RT Kit with gDNA Eraser (Takara); AG SYBR Green Pro Taq HS Premix

Abbreviations. RT, reverse transcription; PCR, polymerase chain reaction; —, not applicable/not reported.

^aThe paper lists GAPDH primers in Table 1 but does not explicitly state which gene was used as the internal reference for normalization.

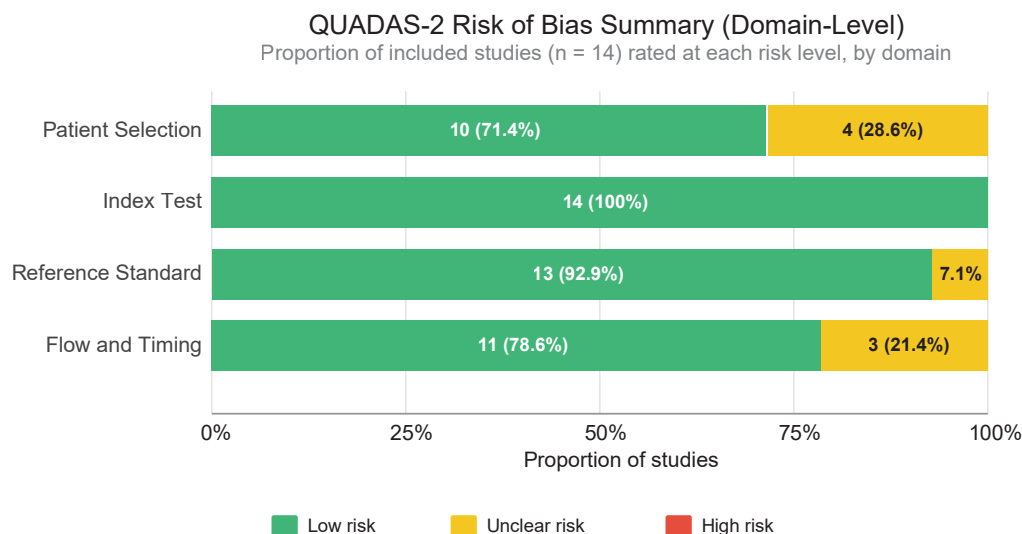


Figure 2. QUADAS-2 Quality Assessment Summary of Included Studies

Risk of bias assessment across four domains: patient selection, index test, reference standard, and flow and timing. Green indicates low risk of bias, yellow indicates unclear risk, and red indicates high risk of bias. In the patient selection domain, 10 studies (71.4%) were at low risk and 4 studies (28.6%) at unclear risk. In the index test domain, all 14 studies (100%) were at low risk. In the reference standard domain, 13 studies (92.9%) were at low risk and 1 study (7.1%) at unclear risk; no studies were at high risk. In the flow and timing domain, 11 studies (78.6%) were at low risk and 3 studies (21.4%) at unclear risk. Overall, 11 studies (78.6%) were rated as low risk and 3 studies (21.4%) as moderate risk of bias.

reported appropriate intervals between index test and reference standard, and all patients received the same reference standard. Three studies (21.4%) were at unclear risk due to incomplete reporting of time intervals or patient exclusions. No studies were at high risk of bias in this domain.

The overall methodological quality of the included studies was good, with 11 studies (78.6%) rated as low risk and 3 studies (21.4%) at moderate risk of bias.

Diagnostic Accuracy of Individual Biomarkers

A total of 14 studies evaluating individual biomarkers for SA-AKI diagnosis were included in the quantitative meta-analysis. These comprised 11 single miRNA marker studies, 1 study reporting the best-performing miRNA from a multi-miRNA panel, and 2 circRNA studies, encompassing 1,840 patients (908 with SA-AKI and 932 controls). The characteristics of all included studies are summarized in Table 1.

Pooled Estimates

The bivariate random-effects meta-analysis of 14 studies yielded a pooled sensitivity of 83.5% (95% CI: 80.7 to 86.0%) and a pooled specificity of 81.5% (95% CI: 77.9 to 84.6%). Forest plots of

pooled sensitivity and specificity are presented in Figure 3. The pooled false positive rate was 18.5% (95% CI: 15.4 to 22.1%). The pooled diagnostic odds ratio (DOR) was 22.29 (95% CI: 16.60 to 29.92). The hierarchical summary receiver operating characteristic (HSROC) model yielded a mean area under the curve (AUC) of 0.885, indicating excellent overall diagnostic accuracy. The SROC curve is presented in Figure 4.

Heterogeneity was low to moderate across studies. For sensitivity, the I^2 was 30.4 to 35.9% (Holling sample size unadjusted approaches), and for specificity, the I^2 was 0.8 to 0.9% (Holling sample size adjusted approaches). The Zhou and Dendukuri approach yielded an I^2 of 0% for both sensitivity and specificity, suggesting that the included studies were relatively consistent in their diagnostic performance.

Publication Bias

Publication bias was assessed using funnel plots, Egger's regression test with sample size as the predictor, Begg's rank correlation test, and trim-and-fill analysis. Visual inspection of the funnel plots (Figure 5A & 5B) revealed approximate symmetry for both sensitivity and specificity, suggesting no substantial publication bias. Egger's test was not

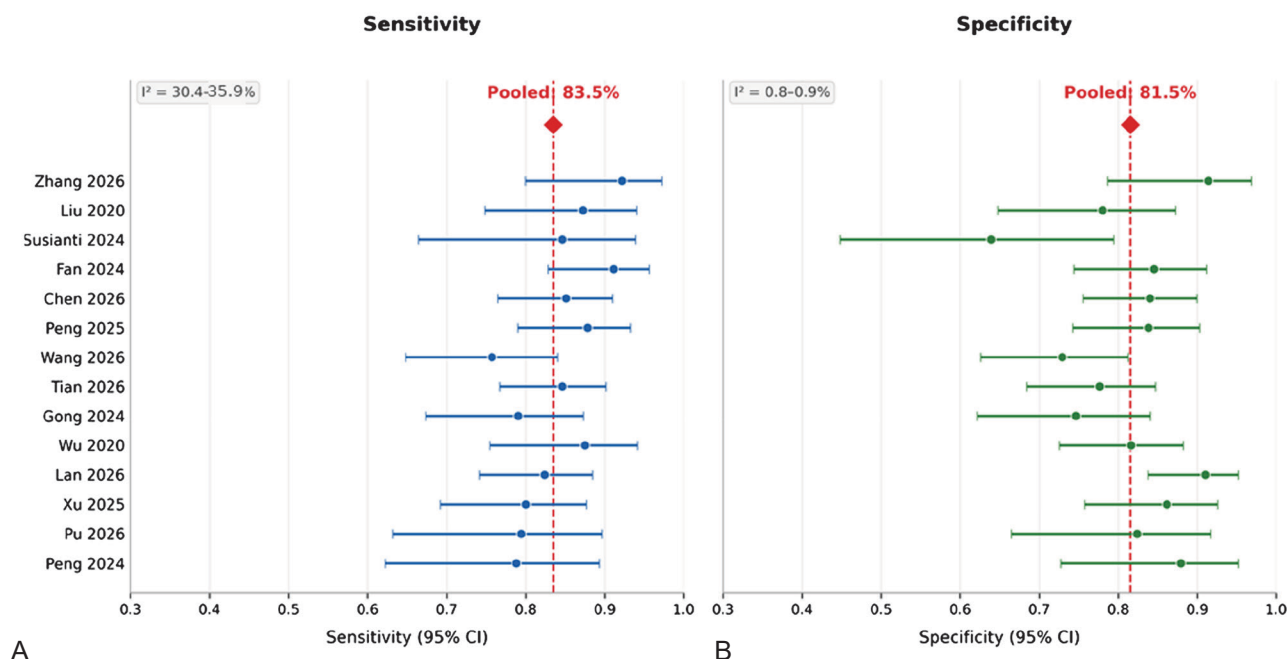
Forest Plot of Sensitivity and Specificity for SA-AKI Biomarkers (n = 14 Studies)

Figure 3. Forest Plots of Pooled Sensitivity and Specificity for Non-coding RNA Biomarkers in Diagnosing SA-AKI (A) Forest plot showing individual study sensitivities with 95% confidence intervals and the pooled sensitivity estimate (diamond). Heterogeneity was low to moderate (I^2 : 30.4 to 35.9%); (B) Forest plot showing individual study specificities with 95% confidence intervals and the pooled specificity estimate (diamond). Heterogeneity was very low (I^2 : 0.8 to 0.9%). The pooled estimates were derived from a bivariate random-effects model of 14 studies (1,840 patients) (AUC = 0.885).

statistically significant for sensitivity ($P = .848$) or specificity ($P = .495$), supporting the absence of small-study effects. Begg's rank correlation test yielded, $P = .157$ for sensitivity; and $P = .079$ for specificity, likewise indicating no significant funnel-plot asymmetry. Trim-and-fill analysis (L0 estimator) identified 2 potentially missing studies for sensitivity, with the adjusted pooled sensitivity (82.6%) remaining close to the original estimate (83.5%). Using the R0 estimator, no missing studies were identified for specificity, and the adjusted pooled specificity (81.5%) was unchanged. These findings suggest that publication bias is unlikely to have substantially influenced the pooled estimates.

Subgroup Analysis

To explore potential sources of heterogeneity and to evaluate the diagnostic performance of biomarkers across different clinical and methodological contexts, we performed subgroup analyses based on sampling time (Early vs. at Diagnosis), sample type (Serum vs. Plasma vs. Urine vs. Serum / Cells), and detection method (SYBR

Green vs. TaqMan). The results of the subgroup analyses are summarized in Table 4.

Subgroup Analysis by Sampling Time

Subgroup analysis based on sampling time revealed that biomarkers measured early (within 24 hours of ICU admission or prior to clinical AKI diagnosis) demonstrated a pooled sensitivity of 83.8% (95% CI: 79.7 to 87.3%) and a pooled specificity of 81.0% (95% CI: 77.0 to 84.5%).

Biomarkers measured at diagnosis (concurrent with clinical AKI diagnosis based on KDIGO criteria) demonstrated a pooled sensitivity of 84.8% (95% CI: 79.8 to 88.8%) and a pooled specificity of 81.6% (95% CI: 69.7 to 89.5%).

Notably, biomarkers measured at diagnosis showed slightly higher sensitivity (84.8 vs. 83.8%) compared to early sampling. However, the confidence intervals for both subgroups overlapped substantially, indicating no statistically significant difference between the two-timing groups. The subgroup analysis by sampling time is presented in Table 4 and Figure 6A.

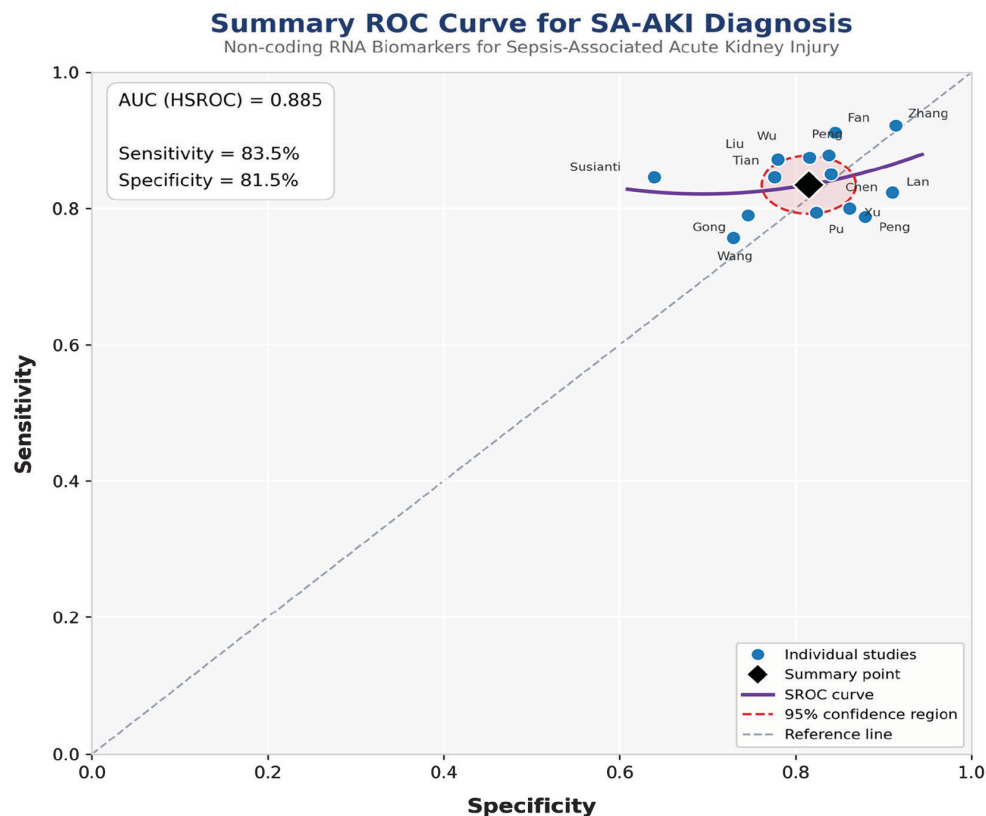


Figure 4. Summary Receiver Operating Characteristic (SROC) Curve for Non-coding RNA Biomarkers in Diagnosing SA-AKI. Blue circles represent individual study estimates. The red diamond represents the summary estimate (sensitivity = 83.5%, specificity = 81.5%). The red dashed ellipse indicates the 95% confidence region. The purple line represents the SROC curve. The area under the curve (AUC) was 0.885, indicating excellent diagnostic accuracy. Analysis included 14 studies with 1,840 patients.

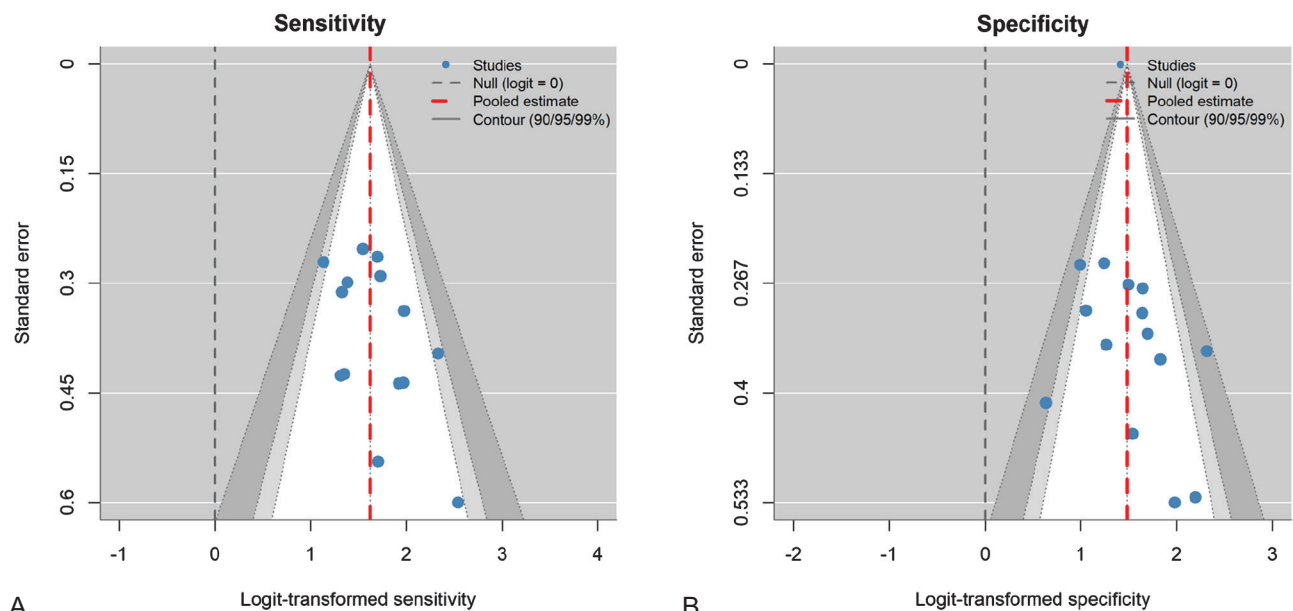


Figure 5. Funnel Plots for Publication Bias Assessment

(A) Funnel plot for logit-transformed sensitivity; (B) Funnel plot for logit-transformed specificity. Blue circles represent individual studies. The grey dashed vertical line marks the null value (logit = 0); the red dashed vertical line marks the pooled estimate. The shaded regions represent the pseudo-90, 95, and 99% confidence contours. Visual inspection of both panels suggests approximate symmetry, consistent with the non-significant Egger's regression test (sensitivity, $P = .848$; specificity, $P = .495$) and Begg's rank correlation test (sensitivity, $P = .157$; specificity, $P = .079$).

Table 4. Subgroup Analysis of Individual Biomarkers

Subgroup	Studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	AUC
Sampling Time				
Early	10	83.8 (79.7–87.3)	81.0 (77.0–84.5)	0.889
At Diagnosis	4	84.8 (79.8–88.8)	81.6 (69.7–89.5)	0.869
Sample Type				
Serum	9	85.1 (80.6–88.6)	79.9 (75.3–83.9)	0.891
Urine	2	83.4 (72.7–90.4)	82.4 (71.1–89.8)	0.895
Plasma	3	81.0 (74.3–86.2)	88.1 (81.4–92.6)	0.868
Detection Method				
SYBR Green	11	83.5 (79.7–86.6)	80.6 (76.5–84.2)	0.888
TaqMan	2	87.5 (79.3–92.8)	80.4 (73.0–86.1)	0.897
Same miRNA (Cross-Study Comparison)				
miR-210 (pooled)	2	89.2 (73.6–96.1)	80.0 (45.9–95.0)	0.918

Abbreviations. CI, confidence interval; AUC, area under the curve.

Note. Values are pooled estimates (%) with 95% CI.

Subgroup Analysis by Sample Type

Subgroup analysis by sample type revealed that serum samples ($n = 9$ studies) demonstrated the highest sensitivity (85.1%, 95% CI: 80.6 to 88.6%) and the highest mean AUC (0.891), with a specificity of 79.9% (95% CI: 75.3 to 83.9%). Plasma samples ($n = 3$ studies) showed the highest specificity (88.1%, 95% CI: 81.4 to 92.6%) but lower sensitivity (81.0%, 95% CI: 74.3 to 86.2%), with a mean AUC of 0.868. Urine samples ($n = 2$ studies) demonstrated balanced diagnostic performance with a sensitivity of 83.4% (95% CI: 72.7 to 90.4%), specificity of 82.4% (95% CI: 71.1 to 89.8%), and mean AUC of 0.895 (Figure 6B).

Subgroup Analysis by Detection Method

Subgroup analysis based on detection method revealed that studies using SYBR Green ($n = 11$ studies) demonstrated a pooled sensitivity of 83.5% (95% CI: 79.7 to 86.6%) and a pooled specificity of 80.6% (95% CI: 76.5 to 84.2%). Studies using TaqMan ($n = 2$ studies) demonstrated a pooled sensitivity of 87.5% (95% CI: 79.3 to 92.8%) and a pooled specificity of 80.4% (95% CI: 73.0 to 86.1%). SYBR Green-based assays showed comparable diagnostic performance to TaqMan assays, with overlapping confidence intervals for both sensitivity and specificity. The subgroup analysis by detection method is presented in Table 4 and Figure 6C.

Same miRNA Cross-Study Comparison (miR-210)

To assess the consistency of diagnostic performance across independent cohorts, we

performed a cross-study comparison of studies evaluating the same miRNA biomarker. Two studies evaluated miR-210 (Zhang *et al.* 2026 and Susianti *et al.* 2024). The pooled sensitivity for miR-210 was 89.2% (95% CI: 73.6 to 96.1%), and the pooled specificity was 80.0% (95% CI: 45.9 to 95.0%). Despite the wide confidence intervals due to the limited number of studies, miR-210 consistently demonstrated good diagnostic performance across both cohorts, supporting its potential as a reliable biomarker for SA-AKI. The cross-study comparison of miR-210 is presented in Table 4.

DISCUSSION

This systematic review and meta-analysis of 14 studies encompassing 1,840 patients demonstrates that circulating microRNAs (miRNAs) and circular RNAs (circRNAs) possess good-to-excellent diagnostic accuracy for sepsis-associated acute kidney injury (SA-AKI), diagnosed according to Sepsis-3³⁶ and KDIGO³⁷ criteria. The pooled sensitivity was 83.5% and specificity was 81.5%, with an HSROC-derived AUC of 0.885. The pooled diagnostic odds ratio of 22.29 indicates that patients with SA-AKI were, on average, more than 20 times more likely to have an elevated biomarker than sepsis patients without AKI — a magnitude comparable to, and in several respects exceeding, that reported for established renal injury biomarkers in critically ill populations.^{9–11} These findings extend a growing body of evidence that non-coding RNAs represent a mechanistically distinct class of injury-responsive biomarkers that

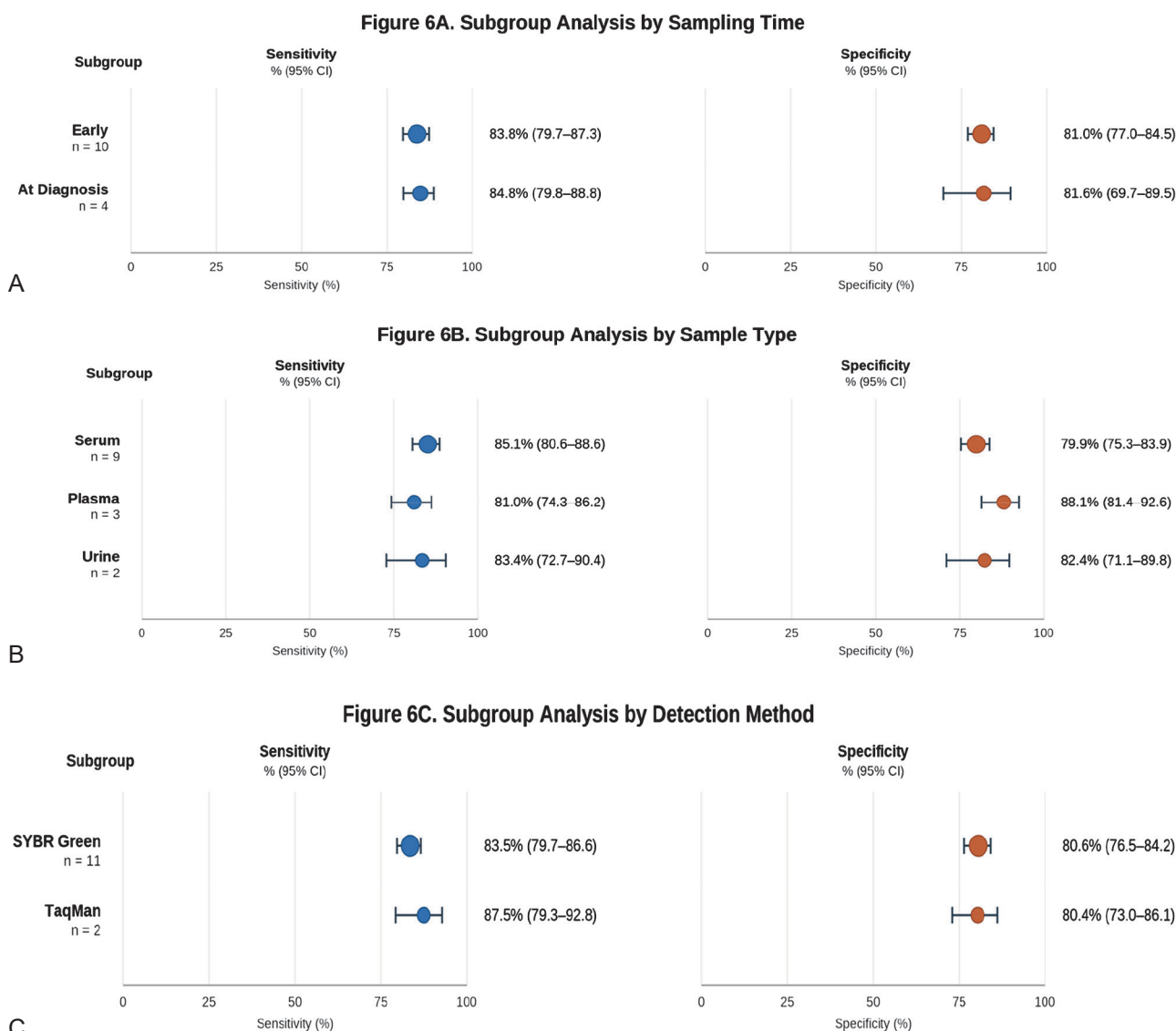


Figure 6. Forest Plots of Subgroup Analyses

(A) Forest plot showing pooled sensitivity and specificity by sampling time (early vs. at diagnosis); (B) Forest plot showing pooled sensitivity and specificity by sample type (serum, plasma, and urine); (C) Forest plot showing pooled sensitivity and specificity by detection method (SYBR Green vs. TaqMan). Error bars represent 95% CI. Subgroup analysis showed comparable performance across sampling times and detection methods, with serum samples demonstrating the highest sensitivity (85.1%) and plasma samples demonstrating the highest specificity (88.1%).

may complement, and in some contexts outperform, conventional markers of kidney function.

SA-AKI remains a major driver of morbidity and mortality in critically ill patients and substantially increases the risk of progression to chronic kidney disease and death.^{1–6} Serum creatinine and urine output, the criteria on which the KDIGO definition of AKI is built, are insensitive to early tubular injury and are confounded by fluid balance, muscle mass, and the physiological trajectory of sepsis itself.^{7,8} This diagnostic lag has motivated a search

for biomarkers capable of detecting injury before functional decline becomes apparent. Protein-based candidates such as NGAL, KIM-1, and the cell-cycle arrest markers TIMP-2•IGFBP7 have been the most extensively studied to date,^{9–11} and a recent our meta-analysis of serum and urinary NGAL specifically in SA-AKI reported pooled accuracy in a broadly similar range to these findings,¹² suggesting that non-coding RNA biomarkers can perform competitively with the most mature protein biomarkers in this field rather than representing a

categorically inferior alternative. Compared with earlier, broader systematic reviews of miRNAs spanning all AKI etiologies,^{23,24} which pooled heterogeneous populations including cardiac surgery; contrast-induced, and sepsis-related AKI together and reported wider, less consistent accuracy estimates, our sepsis-restricted analysis benefits from a more homogeneous clinical context, likely explaining the comparatively narrow confidence intervals around our pooled estimates despite the modest number of included studies. A recent narrative review focused specifically on microRNAs in septic AKI²⁵ similarly concluded that miRNAs are mechanistically well-suited biomarker candidates for this condition, though it did not provide pooled diagnostic accuracy estimates which is a gap the present meta-analysis address directly.

The diagnostic performance observed here is consistent with the underlying biology of the candidate markers. miR-210, the most frequently evaluated biomarker in our dataset and the only one assessed in more than one study, is a well-characterized “hypoxamir” induced by hypoxia-inducible factor-1 α under low-oxygen conditions,^{13,14} a state relevant to both septic microcirculatory dysfunction and tubular hypoxic injury. Its release into the circulation has previously been linked to survival in critically ill patients with AKI,¹⁶ and its consistent performance across the two independent cohorts in our cross-study comparison (pooled sensitivity 89.2%, specificity 80.0%) despite differing countries, sample types, and assay platforms supports genuine biological relevance rather than a single-cohort artifact. miR-21, another prominently studied sepsis-related miRNA, modulates innate immune signaling via TLR4/PDCD4 and has demonstrated organ-protective effects in preclinical models of ischemic preconditioning against sepsis,^{15,17,18} providing mechanistic grounding for its diagnostic signal. circRNAs, meanwhile, are increasingly recognized as stable, protease- and RNase-resistant molecules that act as competing endogenous RNAs; ciRs-126 has previously been shown to predict survival in critically ill AKI patients,²⁰ and the two SA-AKI-specific circRNAs included here (hsa_circ_0072463 and hsa_circ_0056869) have documented regulatory

roles in tubular injury pathways in mechanistic follow-up of the same cohorts.^{21,22} The convergence of plausible mechanism and empirical diagnostic performance strengthens confidence that these associations are unlikely to reflect chance alone.

Between-study heterogeneity was low to moderate depending on the estimation approach, and was negligible under methods designed for the correlated sensitivity–specificity structure of diagnostic accuracy data.^{31,33,38} This consistency was corroborated by our subgroup analyses: neither sampling time (early vs. at diagnosis) nor detection chemistry (SYBR Green vs. TaqMan) significantly altered pooled accuracy, and confidence intervals overlapped substantially across all comparisons. This is clinically reassuring, as it suggests the diagnostic signal is not an artifact of a particular assay platform or a narrow sampling window, and that biomarker measurement obtained either at ICU admission or at the time of clinical AKI diagnosis may be similarly informative. Sample type showed a more interpretable pattern: serum yielded the highest sensitivity and mean AUC, while plasma yielded the highest specificity — a trade-off that may reflect differences in pre-analytical RNA stability and clotting-related contamination between matrices¹⁹ rather than a true difference in underlying biomarker performance, and one that warrants direct head-to-head comparison in future prospective cohorts using matched serum and plasma from the same patients.

The QUADAS-2 assessment indicated generally good methodological quality, with the majority of studies at low risk of bias across all four domains.²⁸ The one domain of concern was the reference standard, where one study was judged unclear risk for not explicitly reporting the AKI diagnostic criteria used; because diagnostic thresholds directly determine case ascertainment, this is the most consequential potential source of bias in the dataset and should be weighted accordingly when interpreting the pooled estimates. Reassuringly, formal assessment of small-study effects did not suggest meaningful publication bias: funnel plots were visually symmetric; Egger’s regression test with sample size as the predictor was non-significant for both sensitivity ($P = .848$) and specificity ($P = .495$),³⁴ Begg’s rank correlation test

was likewise non-significant (sensitivity, $P = .157$; specificity, $P = .079$) ; and trim-and-fill analysis identified only 2 potentially missing studies for sensitivity, with the adjusted pooled estimate (82.6%) remaining close to the original (83.5%) and no missing studies for specificity. Together, these findings indicate that the overall conclusions are unlikely to be driven by selective reporting of positive results.

Several limitations should temper the interpretation of these findings. First, the evidence base remains small: only 14 studies met inclusion criteria, and 12 of 14 individual biomarkers were evaluated in only a single study, precluding meaningful biomarker-specific pooling for any candidate other than miR-210. Second, 13 of the 14 studies (92.9%) originated from China, raising concerns about generalizability to populations with different sepsis epidemiology, genetic backgrounds, and clinical practice patterns; external validation in geographically and ethnically diverse cohorts is a priority for future work. Third, 2×2 contingency data for several studies were back-calculated from reported sensitivity, specificity, and sample size rather than extracted directly from source publications, introducing a small degree of rounding-related imprecision, though this is a common and generally well-tolerated limitation in diagnostic meta-analyses of this type. Additionally, one included study (Fan *et al.*) reported an impossible AUC value of 1.91; we corrected this to 0.910 based on the reported sensitivity and specificity, but this approximation introduces some imprecision. Fourth, considerable methodological heterogeneity existed in RNA extraction kits, normalization strategies (endogenous references ranging from U6 to GAPDH), and detection platforms across studies; despite the reassuring subgroup analysis by detection chemistry, the two-study TaqMan arm is underpowered to rule out unmeasured technical variability. None of the included studies reported head-to-head comparisons against established protein biomarkers such as NGAL or KIM-1 within the same patient cohort, precluding a direct within-study assessment of whether non-coding RNA biomarkers add incremental diagnostic value over, or in combination with, currently available tests. Finally, we did not systematically extract or report whether included studies enrolled patients

with septic shock, excluded them, or included them alongside non-shock sepsis patients. Only 2 of the 14 included studies reported any cohort-level hemodynamic data: Fan *et al.* recorded norepinephrine dosage, and Tian *et al.* reported vasopressor requirement (38.2% in SA-AKI vs. 30.6% in non-AKI). The remaining studies either did not report this information or mentioned septic shock only in the introduction as background. Septic shock is a distinct clinical phenotype within sepsis — defined by Sepsis-3 as sepsis requiring vasopressors plus elevated lactate despite adequate fluid resuscitation — and it carries substantially higher mortality and distinct AKI pathophysiology. Because biomarkers may perform differently in shock versus non-shock sepsis, the generalizability of our pooled estimates to shock-specific or non-shock-specific populations remains uncertain.

Future studies should prioritize external validation of miR-210 and other leading candidates in multi-center, multi-ethnic cohorts using prespecified sampling protocols and standardized normalization strategies to reduce assay-related heterogeneity. Head-to-head or combined-panel studies pairing non-coding RNA biomarkers with NGAL, KIM-1, or established clinical risk scores would clarify whether they offer incremental value as an adjunct rather than a replacement for existing tools. Future diagnostic accuracy studies should also systematically report the proportion of patients with septic shock, vasopressor use, and lactate levels at enrollment, and stratify diagnostic performance by shock status to clarify whether non-coding RNA biomarkers retain their accuracy across the full spectrum of sepsis severity. Given the mechanistic diversity captured here including hypoxia signaling (miR-210), innate immune regulation (miR-21), and circRNA-mediated competing endogenous RNA networks, combination biomarker panels integrating markers from distinct pathophysiological pathways may ultimately outperform any single non-coding RNA, an approach supported by the modestly superior performance of multi-marker panel strategies reported in the broader AKI biomarker literature.

CONCLUSIONS

This metaanalysis demonstrates that circulating

noncoding RNAs, particularly miR210, miR155, miR1323p, and miR7695p, have good to excellent diagnostic accuracy for SAAKI (sensitivity = 83.5%, specificity = 81.5%, AUC = 0.885). Their biological plausibility, stability, and potential for early detection make them promising biomarkers, though the predominance of Chinese studies and lack of headtohead comparisons with established markers warrant caution. Prospective multicenter validation studies are needed before clinical implementation.

DECLARATIONS

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary materials and are available from the corresponding author upon reasonable request.

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Conflict of Interest

Ilad Alavi Darazam serves as members of the RJCCN editorial team. The author had no involvement in the peerreview or editorial decisionmaking processes for this manuscript.

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Author Contributions

F.J.G. conceived the study, designed the protocol, performed data extraction, statistical analysis, and drafted the manuscript. L.L. independently screened studies, verified extracted data, and

contributed to interpretation of results. DG performed data extraction, statistical analysis. I.A.D. Conceptualization, Supervision, Manuscript review & editing and Correspondence with journal. All authors have participated in drafting or editing the manuscript.

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