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Review

Comprehensive analysis of the potential of microRNAs as novel diagnostic biomarkers of placenta accreta spectrum: A systematic review and meta-analysis

[Análisis comprensivo del potencial de los microARN como nuevos biomarcadores diagnósticos del espectro de placenta accreta: Una revisión sistemática y un metanálisis]

Arif B.A. Birru[1]*, Kevin N. Cuandra[2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.
[2]Department of Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.
*E-mail: 2350305215_arif@student.unand.ac.id

Abstract

Context: Placenta accreta spectrum (PAS) is an abnormal pregnancy condition that contributes significantly to maternal mortality and morbidity. Approximately 50-67% of PAS cases are undiagnosed before delivery. Therefore, there is an urgent need to find biomarkers that can be used for early detection so that PAS interventions can be provided promptly to reduce maternal mortality.

Aims: To evaluate the diagnostic accuracy of microRNAs (miRNAs) as biomarkers of PAS.

Methods: A literature search was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). The search was conducted on several databases, including PubMed and ScienceDirect. The risk of bias in the included articles was assessed based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. A random-effects model was used to calculate sensitivity, specificity, positive-likelihood ratio (PLR), negative-likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC). The subgroup analysis was carried out to investigate the heterogeneity. Deeks' funnel plot and Fagan's nomogram were used to evaluate the publication bias clinical application of miRNAs as a PAS diagnostic biomarker, respectively.

Results: Based on three included studies involving 165 PAS cases, the pooled sensitivity, specificity, PLR, NLR, DOR, AUC were 0.90 (95% CI: 0.82-0.95), 0.85 (95% CI: 0.79-0.89), 7.24 (95% CI: 5.42-9.06), 0.33 (95% CI: 0.20-0.46), 72.06 (95% CI: 49.27-94.85), and 0.92 (95% CI: 0.90-0.94). Subgroup analysis showed that using cluster and upregulated miRNA enhances the diagnostic power of miRNA. There is no publication bias in this study (p=0.52).

Conclusions: This study highlights the superior diagnostic accuracy of miRNAs in diagnosing PAS, indicating their potential as valuable biomarkers for detecting PAS.

Keywords: biomarker; diagnostics; meta-analysis; microRNAs; placenta accreta spectrum.

Resumen

Contexto: El espectro de placenta acreta (PAS) es una afección anormal del embarazo que contribuye significativamente a la mortalidad y morbilidad maternas. Aproximadamente entre el 50% y el 67% de los casos de PAS no se diagnostican antes del parto. Por lo tanto, existe una necesidad urgente de encontrar biomarcadores que permitan la detección temprana, de modo que se puedan implementar intervenciones oportunas para reducir la mortalidad materna.

Objetivos: Evaluar la precisión diagnóstica de los microARN (miARN) como biomarcadores de PAS.

Métodos: Se realizó una búsqueda bibliográfica basada en los Elementos de Informe Preferidos para la Revisión Sistemática y el Metaanálisis (PRISMA). La búsqueda se realizó en varias bases de datos, incluyendo PubMed y ScienceDirect. El riesgo de sesgo en los artículos incluidos se evaluó con la herramienta de Evaluación de la Calidad de los Estudios de Precisión Diagnóstica-2 (QUADAS-2). Se utilizó un modelo de efectos aleatorios para calcular la sensibilidad, la especificidad, la razón de verosimilitud positiva (RPP), la razón de verosimilitud negativa (RPN), la razón de probabilidades diagnósticas (ORD) y el área bajo la curva (AUC). Se realizó un análisis de subgrupos para investigar la heterogeneidad. Se utilizaron el gráfico de embudo de Deeks y el nomograma de Fagan para evaluar el sesgo de publicación en la aplicación clínica de los miRNA como biomarcador diagnóstico de PAS, respectivamente.

Resultados: Con base en tres estudios incluidos que incluyeron 165 casos de PAS, la sensibilidad, especificidad, PLR, NLR, DOR y AUC agrupados fueron de 0,90 (IC del 95%: 0,82-0,95), 0,85 (IC del 95%: 0,79-0,89), 7,24 (IC del 95%: 5,42-9,06), 0,33 (IC del 95%: 0,20-0,46), 72,06 (IC del 95%: 49,27-94,85) y 0,92 (IC del 95%: 0,90-0,94). El análisis de subgrupos mostró que el uso de miRNA agrupados y sobreexpresados mejora su capacidad diagnóstica. No existe sesgo de publicación en este estudio (p=0,52).

Conclusiones: Este estudio destaca la superior precisión diagnóstica de los miRNA en el diagnóstico de PAS, lo que indica su potencial como valiosos biomarcadores para su detección.

Palabras Clave: biomarcador; diagnóstico; espectro de placenta acreta; metaanálisis; microARN.

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AUTHOR INFO
ORCID: 0009-0001-4589-7072 (ABAB)
0009-0007-7785-7474 (KNC)

Abbreviations: AUC: Area under the curve; DOR: Diagnostic odds ratio; microRNAs: miRNAs; NLR: Negative-likelihood ratio; PAS: Placenta accreta spectrum; PLR: Positive-likelihood ratio; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis.

INTRODUCTION

Placenta accreta spectrum (PAS) refers to the penetration of trophoblastic tissue through the decidua basalis into the uterine myometrium, uterine serosa, or extending into the parametrium or adjacent pelvic organs. This abnormal pregnancy condition is a significant contributor to maternal mortality and morbidity. Based on epidemiological data, the prevalence of PAS is 2.5% and is expected to increase annually due to the increasing rate of cesarean delivery, which is a significant risk factor for PAS in subsequent pregnancies (Guo et al., 2022). Adverse pregnancy outcomes caused by PAS include severe hemorrhage, hysterectomy, and urinary tract injury, which have a significant impact on long-lasting psychosocial and emotional problems and decreased quality of life (Einerson et al., 2023).

PAS was known to lack typical clinical manifestations and laboratory indicators for effective screening. Approximately 50-67% of PAS cases are undiagnosed before delivery (Jauniaux et al., 2018). Commonly, high maternal risk factors for PAS combined with prenatal ultrasound or MRI are used to diagnose PAS (Do et al., 2020; Jauniaux et al., 2018). However, such imaging is relatively costly and has technical limitations. Prenatal ultrasound has false-negative reports for PAS cases that have low implantation sites and in the posterior uterine wall, and contrast agents are rarely used in pregnant women. In addition, pathological analysis of the separated placenta after delivery (the gold standard for PAS diagnosis) cannot provide timely results, and there is also the possibility of false negatives caused by incomplete separation of the placenta from the uterus (Jauniaux et al., 2018). Therefore, there is an urgent need to find biomarkers that can be used for early detection so that PAS interventions can be provided promptly to reduce maternal mortality.

Along with technological developments in diagnostics, microRNAs (miRNAs) have attracted much attention in recent decades. miRNAs are integral components of biological tissues that regulate gene expression (O'Brien et al., 2018). miRNAs are short non-coding RNA segments, ~20-25 nucleotides in length, that can suppress translation of target mRNAs or induce messenger RNA (mRNA) silencing through binding to seed sequences in one or more 3' untranslated regions of target mRNAs. A single miRNA can affect multiple genes regulating cellular events and pathways (O'Brien et al., 2018). Circulating miRNA levels have been reported to be transported in blood exosomes, extracellular microvesicles, Argonaute2, and other proteins that protect them from being degraded. This is why circulating miRNAs can be used as diagnostic biomarkers.

Research conducted by Timofeeva et al. (2024) showed that quantitative assessment of miRNA-320b, let-7d-5p, miRNA-629-5p, and miRNA-17-5p in female blood plasma can significantly identify PAS with high specificity (93-100%) and sensitivity (78-97%). Another study by Chen et al. (2020) showed that miRNA-196a-5p, miRNA-518a-3p, miRNA-139-3p, and miRNA-671-3p in PAS patients were significantly downregulated. The use of the four single miRNAs had AUC values ranging from 0.59 to 0.74, sensitivity ranging from 0.54 to 0.80, and specificity ranging from 0.62 to 0.76.9. From these various results, it is clear that miRNAs are promising diagnostic biomarkers.

miRNAs have several benefits over other biomarkers. First, miRNAs are very stable, which makes it simple to collect, store, and transport them without deterioration (Kupec et al., 2022). Second, due to their superior sensitivity, miRNAs may provide more precise early disease identification compared to conventional PAS biomarkers (Condrat et al., 2020). Lastly, miRNA identification is flexible and helpful for prognostic evaluation and therapy impact prediction (Hill and Tran, 2021). Consequently, many studies have been done on the potential of miRNAs as novel biomarkers for diagnosing PAS, which has given their clinical application a solid scientific basis. However, the number of miRNAs identified has mixed and inconclusive results. There are also no systematic reviews and meta-analyses that discuss the potential of miRNAs as biomarkers of the latest PAS diagnosis. Therefore, this study aimed to examine the diagnostic accuracy of miRNAs as novel diagnostic biomarkers of the placenta accreta spectrum.

MATERIAL AND METHODS

Eligibility criteria and PICOS strategy

A literature search was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Page et al., 2021). The PICOS strategy is presented in Table 1.

The inclusion criteria in this study were: (1) the article was research on miRNA in humans; (2) the article had a randomized controlled trial, experimental, or observational research design; (3) it contained the keyword placenta accreta spectrum in the

Table 1. The PICOS strategy

PICOS	Description
Participants	The population undergoing diagnostic testing was divided into the PAS and the normal control group.
Intervention	miRNA levels in the blood serum of patients.
Comparison	Histology findings as a gold standard test.
Outcome	Quantitative measures for diagnostic test accuracy, including sensitivity, specificity, positive-likelihood ratio (PLR), negative-likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC).
Study design	Case-control and cohort studies

title or abstract. Meanwhile, the exclusion criteria included (1) studies published more than five years ago, (2) studies in languages other than English, (3) inappropriate study design, and (4) articles with incomplete or unextractable data.

Information sources

On 18th September 2024, two investigators (ABAB and KNC) independently conducted abstract and full-text screening using inclusion-exclusion criteria to identify eligible studies in PubMed and ScienceDirect databases. Additionally, a "snowball" strategy was carried out on 25th September, 2024. To locate additional studies, this entailed carefully examining the reference lists of publications that qualified for a full-text review and using Google Scholar to find and examine studies that cited them.

Search strategy

A literature search was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). The search was conducted on several databases, including PUBMED and ScienceDirect, by searching for studies published in the last five years with the following keywords:

1. Search: ("microRNA" OR "miRNA" OR "miR" OR "miRNAs")
2. Search: ("Placenta Accreta Spectrum" OR "PAS")
3. Search: ("Diagnosis" OR "Early Detection")
4. Search: ("Specificity" OR "Sensitivity")
5. Search #1 AND #2 AND #3 AND #4

Selection process

Two separate researchers (ABAB and KNC) thoroughly reviewed the titles and abstracts as part of the selection process. Discussions were held to settle disagreements until a consensus was reached. Next, the researchers screened each retrieved abstract and title article independently in pairs. In cases of disagreement during the study selection process, an independent third-party expert was consulted to provide an impartial evaluation and help resolve any disputes between the authors.

Data collection process and data items

Two investigators (ABAB and KNC) independently conducted data extraction from the inclusion studies. The data extraction form was designed based on a previous study (Hasani et al., 2024). After comparing the extracted data, any differences were discussed and settled. ABAB double-checked the accuracy of the data before entering it into the STATA/BE (v.18.0) statistical software. The extracted data includes: (1) first author; (2) publication date; (3) study design; (4) name of miRNA; (5) miRNA regulation mode; (6) number of case and control participants; (7) quantitative measure of diagnostic tools (sensitivity, specificity, and AUC).

Study risk of bias assessment

The two review authors (ABAB and KNC) independently applied the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which includes criteria for patient selection, index test, flow and timing, and reference standard, using Review Manager (RevMan) 5.3 software. As a result, the appraisal outputs classified the applicability and bias risks as unclear, low, or high.

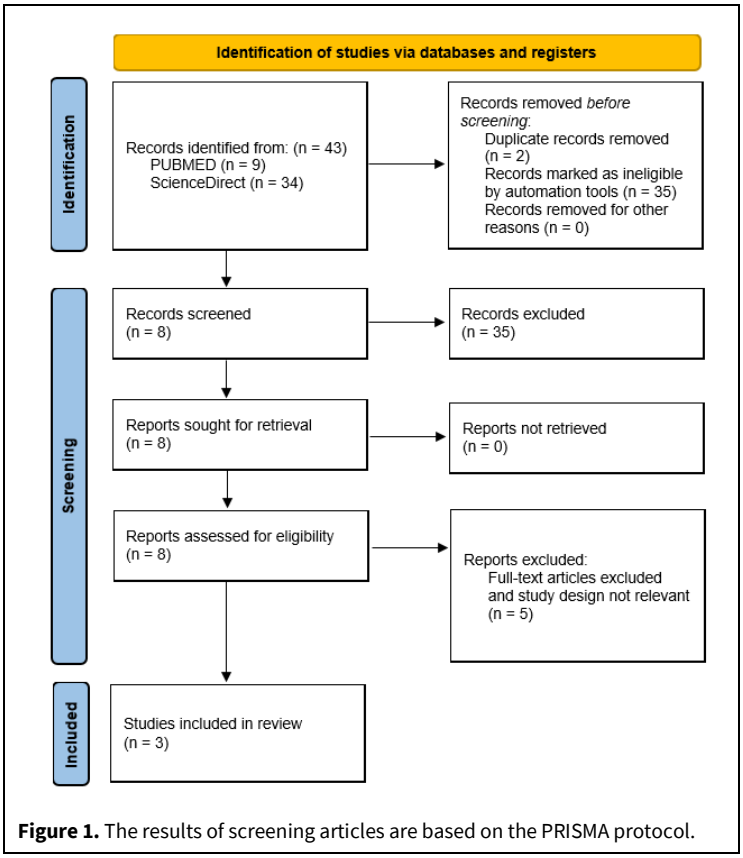

Figure 1. The results of screening articles are based on the PRISMA protocol.

Until the two review authors came to an agreement, disagreements regarding bias risk assessments and the justifications for these assessments were settled by discussion. In cases of disagreement during the risk of bias assessment, an independent third-party expert was consulted to provide an impartial evaluation and help resolve any disputes between the authors.

Effect measures and synthesis methods

Meta-analysis was performed using STATA/BE (v.18.0) statistical software. A random-effects model was used to calculate sensitivity, specificity, positive-likelihood ratio (PLR), negative-likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) with 95% confidence interval (95% CI). The specificity and sensitivity of miRNA combinations from different studies will be assessed using forest plots and a summary receiver operating characteristic (SROC) curve. Cochrane's Q test and I^2 statistics were used to evaluate for statistical heterogeneity between studies (Belete et al., 2024). Furthermore, subgroup analysis was carried out to investigate the heterogeneity. Deeks' funnel plot was used to evaluate the publication bias. The p-value >0.05 indicates that there is no publication bias. Fagan's nomogram was used to assess the clinical application of miRNAs as a PAS diagnostic biomarker (Belete et al., 2024).

RESULTS

Study selection and characteristics

Fig. 1 describes the study selection process based on the PRISMA protocol. The initial search of two databases resulted in 43 articles. The screening continued with the automation tool dropping duplicate and ineligible articles, resulting in eight articles. The eight articles in the previous stage were assessed based on inclusion and exclusion criteria, resulting in three studies that met the criteria in this study. The results of data extraction are shown in Table 2. The three eligible articles included 165 PAS cases and 352 controls. Two of the three eligible articles were cohort articles. All miRNAs used were miRNAs derived from serum. Half of the articles' data were single miRNAs, and the other half were clusters of miRNAs.

Risk of bias in studies

The QUADAS-2 tool quality assessment findings (Yang et al., 2021) indicate that the included studies generally validated and enhanced methodological requirements, with a low risk of bias and applicability issues across most quality appraisal categories (Fig. 2).

Table 2. Data extraction results from included studies.

No.	Author, year	Type of study	Sample	Case/ Control	miRNA	Down/Up-regulation	Sens	Spec	AUC
1.	Timofeeva, 2024	Cohort	Blood serum	32/14	miRNA-17	Up	0.94	0.71	0.87
					miRNA-92a	Up	0.91	0.86	0.9
					miRNA-17, 629	Up	0.78	1.00	0.91
					miRNA-320b	Up	0.88	0.86	0.91
					miRNA-26, 17	Up	0.88	0.93	0.91
					miRNA-320b, 92a	Up	0.97	0.93	0.96
					miRNA-92a, 26a, 16	Up	1.00	0.84	0.97
					miRNA-26a, 17	Up	1.00	0.82	0.96
					miRNA-26a, 101	Up	1.00	0.84	0.95
					miRNA-92a, 17	Up	0.9	0.9211	0.94
					miRNA-320a, 17	Up	0.8	0.97	0.93
					miRNA-26a	Up	1.00	0.84	0.92
					miRNA-101	Up	0.80	0.79	0.92
2.	Munoz, 2024	Cohort	Blood serum	60/60	miRNA-92a, 103, 192	Up	0.892	0.80	0.81
3.	Chen, 2020	Case-Control	Blood serum	73/113	miRNA-139, 196a, 518a, 671	Down	0.77	0.92	0.91
					miRNA-139	Down	0.80	0.62	0.73
					miRNA-196a	Down	0.69	0.66	0.74
					miRNA-518a	Down	0.54	0.69	0.59
					miRNA-671	Down	0.57	0.76	0.70

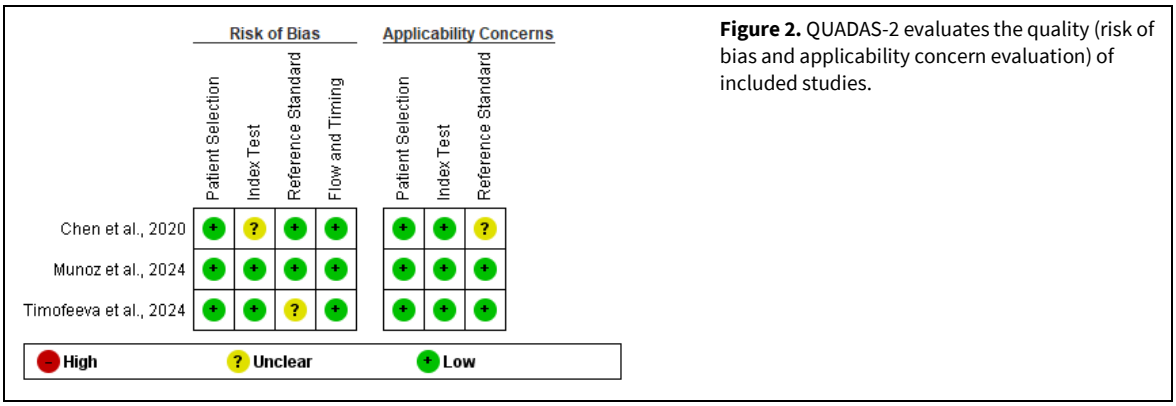

Figure 2. QUADAS-2 evaluates the quality (risk of bias and applicability concern evaluation) of included studies.

Diagnostic accuracy of miRNAs as diagnostic biomarkers of PAS

The analysis results of the three studies that met the criteria showed that the I^2 value was 84.6%. This indicates that there is a high heterogeneity among studies in this study (I^2>50%), so this meta-analysis uses a random effect model (I^2 = 86.43). The meta-analysis model showed that miRNAs had a pooled sensitivity of 0.90 (95% CI: 0.82-0.95, p<0.000), a pooled specificity of 0.85 (95% CI: 0.79-0.89, p<0.000), PLR of 7.24 (95% CI: 5.42-9.06), NLR of 0.33 (95% CI: 0.20-0.46), and DOR of 72.06 (95% CI: 49.27-94.85) in a diagnostic evaluation involving 165 PAS cases and 352 controls (Fig. 3). These results showed that miRNAs could distinguish PAS from non-PAS patients. In addition, the AUC was 0.92 (95% CI: 0.90-0.94), which suggested that the circulating miRNAs had an outstanding diagnostic accuracy for PAS (Fig. 4).

Subgroup analysis

Using sensitivity (0.95 vs. 0.85), specificity (0.91 vs. 0.76), PLR (10.70 vs. 3.81), NLR (0.18 vs. 0.42), DOR (4.45 vs. 2.49), and AUC (0.90 vs. 0.78), subgroup studies revealed that the miRNA cluster outperformed single miRNA in terms of diagnostic accuracy. Furthermore, the following diagnostic values showed that upregulation types outperformed downregulation types: AUC (0.89 vs. 0.70), DOR (4.14 vs. 1.86), specificity (0.88 vs. 0.75), PLR (8.66 vs. 3.56), NLR (0.17 vs. 0.49), and sensitivity (0.95 vs. 0.68).

Applicability of miRNAs in clinical use

Based on Fagan's nomogram, our results showed that given a pre-test chance of 25%, a positive diagnostic test result would increase the post-test probability of an individual having PAS to almost 79%. This indicates patients' likelihood of having PAS rises to 79% if their test results use miRNA biomarkers. On the other hand, a negative test result would reduce the post-test probability to about 2%, indicating that the condition is almost specific to be ruled out by a negative PAS using a miRNA test. This suggests miRNAs potentially apply as a PAS diagnostic biomarker (Fig. 5).

Publication bias

Deek's funnel plot asymmetry test assesses publication bias in meta-analyses. A significant p-value ($p<0.05$) indicates evidence of asymmetry, suggesting potential publication bias. However, our study showed no publication bias (p=0.52) (Fig. 6).

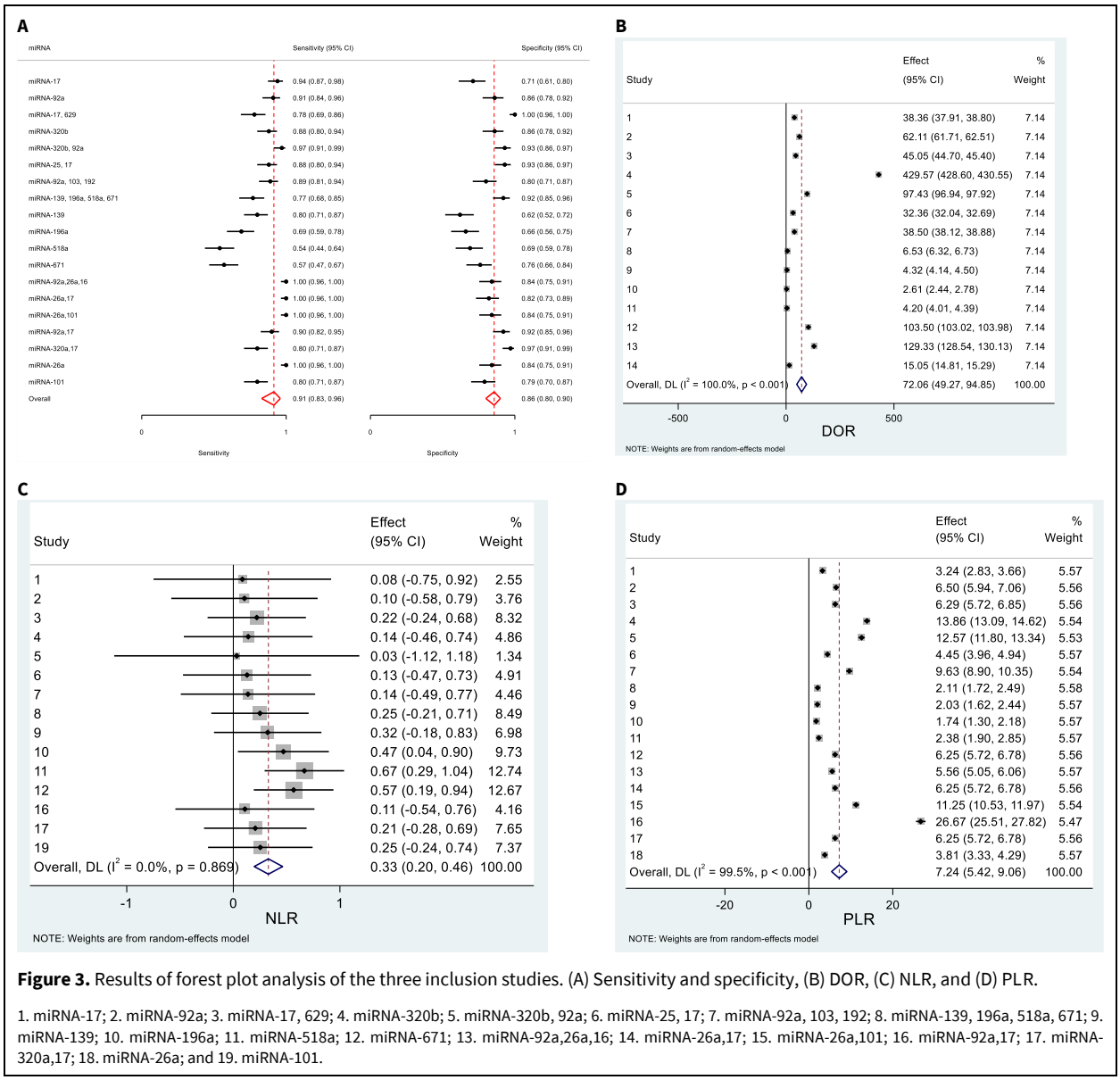

Figure 3. Results of forest plot analysis of the three inclusion studies. (A) Sensitivity and specificity, (B) DOR, (C) NLR, and (D) PLR.

1. miRNA-17; 2. miRNA-92a; 3. miRNA-17, 629; 4. miRNA-320b; 5. miRNA-320b, 92a; 6. miRNA-25, 17; 7. miRNA-92a, 103, 192; 8. miRNA-139, 196a, 518a, 671; 9. miRNA-139; 10. miRNA-196a; 11. miRNA-518a; 12. miRNA-671; 13. miRNA-92a,26a,16; 14. miRNA-26a,17; 15. miRNA-26a,101; 16. miRNA-92a,17; 17. miRNA-320a,17; 18. miRNA-26a; and 19. miRNA-101.

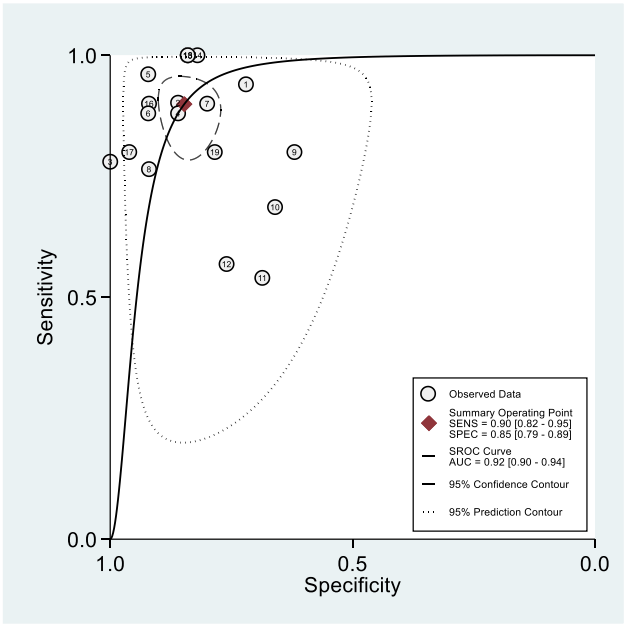

Figure 4. Summary ROC (SROC) results of the three inclusion studies.

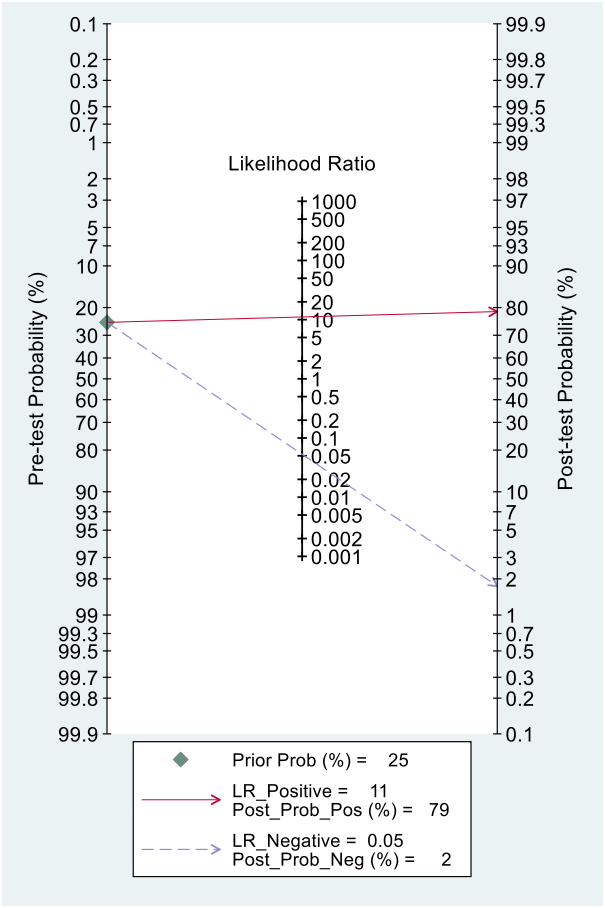

Figure 5. Fagan's nomogram displays post-test probabilities under a 25% pre-test probability.

DISCUSSION

PAS remains a significant contributor to maternal mortality and morbidity. The high mortality and morbidity of PAS are due to the challenging diagnosis of PAS to date. Advanced clinical examinations, including ultrasonography and, in some cases, MRI imaging, can diagnose severe PAS with high sensitivity (88-97%) when used by skilled personnel (Yu and Leung et al., 2020). However, antenatal identification of PAS is still limited and is reported in only 33% of cases (Yu and Leung et al., 2020). With these limitations, efforts are needed to find new biomarkers to help diagnose PAS as early as possible. As a new method to diagnose PAS, circulating miRNAs in serum and plasma is a non-invasive method, and it is easy to obtain samples and relatively cheap.

In this study, the results of a meta-analysis of three studies using forest plots showed that miRNAs had a combined sensitivity and specificity of 90% (95% CI: 0.83-0.96, p<0.000) and 85% (95% CI: 0.80-0.90, p<0.000), PLR of 7.24 (95% CI: 5.42-9.06), NLR of 0.33 (95% CI: 0.20-0.46), and DOR of 72.06 (95% CI: 49.27-94.85). miRNAs circulating in plasma and serum were found to distinguish PAS patients from healthy controls, and their diagnostic accuracy in PAS reached a high level as a diagnostic evaluation criterion. This was demonstrated by the SROC curve drawing and the corresponding AUC value of 0.92 (95% CI: 0.90-0.94).

The diagnostic efficacy of miRNAs is further supported by their high PLR and low NLR (Dormuth et al., 2016; Schlattmann, 2023). Notably, compared to healthy control patients, our study's PLR value of 7.24 indicates a roughly 7-fold increased risk of identifying PAS. However, the NLR value of 0.33 suggests that the likelihood of getting PAS is just 3.3% among individuals who tested negative. Furthermore, a DOR >1 and an AUC close to 1 indicate the best distinguishing power and overall test efficacy (Belete et al., 2024; Dormuth et al., 2016). Our results of a DOR of 72.06 and an AUC value of 0.92 confirm the remarkable ability of miRNA markers to distinguish PAS from healthy individuals. These results demonstrate that miRNAs can potentially be reliable and accurate diagnostic biomarkers for PAS.

Our subgroup analysis results also illustrate a significant difference in diagnostic accuracy when considering different miRNA profiling and regulation types. miRNAs cluster and upregulated miRNAs showed better diagnostic accuracy than single and downregulated miRNAs, with AUC values of 0.90 vs. 0.78 and 0.89 vs. 0.70, respectively. Such variation might be attributable to sample size-induced bias and statistical power (Serdar et al., 2021).

Fagan's nomogram analysis shows a positive likelihood ratio (PLR) of 0.79 and a negative likelihood ratio (NLR) of 0.02 (Caraguel and Venderstichel, 2013). This indicates that positive test results for miRNAs suggest a 79% chance of developing PAS. Conversely, negative miRNA results lower the likelihood to about 2%. These results highlight the promising diagnostic potential of miRNAs in distinguishing individuals with PAS from healthy individuals, providing strong evidence for their use in both exclusion and confirmation of PAS. This diagnostic capability of miRNAs is crucial and encouraging, addressing the growing concerns about current diagnostic methods and facilitating early and accurate detection.

In practice, miRNAs could offer an early, non-invasive method for detecting PAS, potentially improving early diagnosis. It could also allow for better risk stratification of pregnant women, leading to tailored monitoring and early interventions, ultimately improving maternal and fetal outcomes. miRNAs could be integrated into routine prenatal care, enhancing diagnostic accuracy and facilitating personalised treatment plans. From a policy perspective, positive results could influence clinical guidelines and make miRNA a standard part of prenatal screening, especially in high-risk pregnancies. This approach could be more cost-effective than conventional diagnostic methods, reducing long-term healthcare costs and improving access to care.

This meta-analysis is the first to thoroughly explore the potential of miRNAs for diagnosing PAS. While analysing a broad range of miRNAs from studies with high methodological quality is a strength, there are some limitations. First, the metadata is limited due to varying cutoff values for the miRNAs, which may lead to significant heterogeneity among the included studies. These findings might be affected by decreased statistical power because most eligible articles have small sample sizes. The few available studies hindered our capacity to collect enough data on the role of miRNAs as indicators of disease severity or predictors of PAS. While the limitations mentioned may have affected the results, we believe they provide a strong foundation for future research. Therefore, this study strongly encourages future researchers to validate and support our conclusions by conducting comprehensive studies with consistent methodologies and larger sample sizes.

CONCLUSION

This study highlights the superior diagnostic accuracy of miRNAs in differentiating PAS patients from normal pregnancy patients, indicating their potential as valuable biomarkers for detecting PAS. It is well recognised that using cluster and upregulated miR-

NAs enhances the capacity and capability of miRNAs to diagnose PAS. However, to validate the clinical utility of miRNAs in PAS diagnosis, comprehensive, high-quality methodological studies incorporating both miRNAs and miRNA panel evaluations must be carried out. miRNAs could be used in clinical practice to supplement current diagnostic techniques, such as providing a quick, accurate, and non-invasive alternative method, especially in settings with limited resources. Subsequent investigations must focus on harmonising miRNA identification methodologies and verifying these results in various demographics and conditions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Birru ABA	Cuandra KN
Concepts or ideas	x	
Design	x	x
Definition of intellectual content	x	
Literature search	x	x
Experimental studies	x	x
Data acquisition		x
Data analysis	x	x
Statistical analysis		x
Manuscript preparation	x	x
Manuscript editing	x	x
Manuscript review	x	x

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