Acta Biologica Szegediensis

Volume 66(1):29-36, 2022
Acta Biologica Szegediensis
http://abs.bibl.u-szeged.hu/index.php/abs

DOI:10.14232/abs.2022.1.29-36

ARTICLE

Expression of circulating microRNAs as diagnostic markers of preeclampsia: a meta-analysis

Alayasa Nadeim N. I.*, Tatiana Pavlovna Shkurat

South Federal University, Rostov-on-Don, Russia

ABSTRACT Pre-eclampsia (PE) is defined as a severe gestational condition that appears after the twentieth weeks of pregnancy, affecting 5-8% worldwide. Circulating microRNAs are short, noncoding RNA molecules. The role of miRNAs was studied in many publications related to PE; however, the results have been inconsistent due to variety of diagnostic and prognostic values. Therefore, we conducted a meta-analysis study to quantify the general diagnostic effects of circulating miRNAs in the diagnosis of PE. We searched chosen databases and systematically collected publications for analysis from January 2017 till June 2021. Following the screening of the literature and the extraction of data. After that, we conducted a quality evaluation using the QUADAS-2 score system. A bivariate-random effect meta-analysis model was then used to construct the pooled diagnostic parameters. To identify the causes of heterogeneity, we conduct the threshold effect analysis as well as the subgroup analysis. Fagan`s Nomogram was used to validate the clinical utility. Moreover, sensitivity and specificity analysis were used to evaluate each study's reliability, and to investigate the publication-bias we conducted the funnel plot asymmetry test. Our meta-analysis involved 8 articles, containing in total 704 pregnant women, 354 pre-eclampsia patients and 350 uncomplicated, normal pregnancy. According to the results, the total pooled results of sensitivity, specificity, and DOR were as follows: 0.88 (95% CI: 0.86-0.90), 0.87 (95% CI: 0.85-0.89) and 57.54 (95% CI: 35.24-93.94), respectively. Moreover, subgroup analysis indicated that non plasma samples and non-Asian ethnicity had higher diagnostic value, however we didn't conduct a subgroup-analysis for the internal references subgroup due to inadequate data. We concluded that the circulating miRNAs could be used as a screening tool for pre-eclampsia diagnosis. Our meta-analysis shows that circulating microRNAs serve as PE biomarkers because of their high sensitivity and specificity. In addition, further studies using a bigger sample size is needed for better assessment of miRNAs in the diagnosis of pre-eclampsia.

Acta Biol Szeged 66(1):29-36 (2022)

KEY WORDS

diagnostic
meta-analysis
microRNA
pre-eclampsia

ARTICLE INFORMATION

Submitted
20 December 2021.
Accepted
05 April 2022.
***Corresponding author**
E-mail: alayasa.nadeim@gmail.com

Introduction

Pre-eclampsia (PE) is described as a serious gestational syndrome that appears after 20th weeks of pregnancy or immediately after delivery (Abdi et al. 2018; Gathiram and Moodley 2016). It is still one of the leading causes of both maternal and perinatal morbidity and mortality, with a rate of 5-8% of pregnancies, and is directly associated with 15% of maternal deaths world-wide, but its prevalence varies greatly from country to country (Duley 2009; Jim and Karumanchi 2017; Nankali et al. 2013). PE is characterised by thrombocytopenia, maternal hypertension, proteinuria, and by other pregnancy systemic conditions appearing in the 2nd or 3rd trimester of pregnancy, at delivery or immediately after birth (Dekker 2002; Spence et al. 2021). Different options exist for the classification of PE, based on the major clinical symptoms. The most common classification is that developed by the American Association of Obstetricians and Gynaecologists (ACOG Committee on Practice Bulletins--Obstetrics 2002) which defines mild PE as elevated maternal systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg (on two times by 6 h interval), accompanied by significant proteinuria (≥ 300 mg/24 h) after twenty weeks' gestation. Severe PE, on the other hand, is defined by elevations of SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg on at least 2 times by 6 h apart, long side mild hypertension, accompanied by severe proteinuria (≥2 g/24 h or ≥2+ using a dipstick) (Jairajpuri and Almawi 2016; Lv et al. 2019; Murphy et al. 2015; Wheeler and Jones 1981). It is widely accepted that PE occurs asymptomatically, characterised by defects in trophoblast invasion and spiral artery remodelling in the first trimester, leading to abnormal placentation, which results in placental ischaemia and maternal PE syndrome in later gestation-phase (Li et

al. 2013). Despite considerable advances in PE studies, it remains a challenge to make an early assessment to predict the risk of PE. Presently many studies are dedicated to find and determine various molecular genetic markers of PE (Murphy et al. 2017; Vashukova et al. 2020). One direction that is fast evolving is the study of microRNAs.

MicroRNAs (miRNAs) defined as a class of short, endogenous, non-coding RNA molecules, 18-24 nt long, that affect the post-transcriptional regulation of gene expression via suppressing translation or promoting degradation of their target mRNAs (Wu et al. 2021). They target the RNA-induced silencing complex to complementary sites in their target mRNAs' 3′-untranslated region (UTR). Translational repression and/or degradation of the targeted mRNA occurs depending on the degree of base pairing between the miRNA and the 3′-UTR. MiRNAs are known to regulate a variety of physiological processes, and their de-regulation is a pathological mechanism in many diseases, including PE (Bounds et al. 2017). Deregulated miRNAs have been linked to all aspects of placentation, including trophoblast proliferation, differentiation, and invasion, endothelial cell activity, and the inflammatory response (Munaut et al. 2016). Placental tissue expresses miRNAs during pregnancy, and their concentration differs based on the gestational week and placental stage development, highlighting their significance in placental regulation (Mouillet et al. 2011).

Several studies have proven the role of circulating miRNAs in PE, but with contradictory results due to varying diagnostic and prognostic values. These contradictory results can be associated with many factors, including ethnicity, specimen type, and microRNA profiling (Lip et al. 2020). We conducted a meta-analysis in this study to investigate the role of circulating miRNAs in PE diagnosis.

Materials and methods

Databases search

We carried out a diagnostic meta-analysis using the PRISMA guidelines (McInnes et al. 2018). Databases searched included PubMed, Web of Science (WOS), Embase, Google Scholar, and Cochrane Library and were searched between January 2017 and June 2021. The following search keywords were used to find relevant data: ("preeclampsia" OR "pre-eclampsia" OR "pre eclampsia" OR "eclampsia" OR "gestational hypertension" OR "pregnancy hypertension" OR "pregnancy toxemia" OR "gestational hypertensive disorder" OR "hypertensive disorders of pregnancy" OR "pregnancy-associated hypertension OR "pregnancy-induced hypertension") AND ("miR" "microRNAs" OR "miRNAs" OR "microRNA" OR "miRNA") AND ("specificity" OR "sensitivity" OR "ROC curve"). Further, we reviewed the reference-lists of all relevant articles for any publications that could be eligible for inclusion.

Inclusion and exclusion criteria

The inclusion criteria were defined as follows based on the existing methods of diagnostic meta-analysis: 1) Observation-based studies on pregnancies women with pre-eclampsia; 2) Studies related to circulating miRNAs and pre-eclampsia; 3) PE patients were diagnosed using the widely accepted gold reference standard: blood pressure of 140/90 mmHg and proteinuria of 0.3 g/day after 20 weeks of gestation. 4) The studies that clearly reporting sensitivity, specificity with 95% confidence interval or contain sufficient data to make a 2*2 table for calculating the following values (value of true positives, value of false positives, value of false negatives, and value of true negatives). Contrarily, the criteria for exclusion was as follows: 1) Duplicate publication; 2) Reviews, Abstracts, Editorial, Conference and Notes; 3) If the expression-level of microRNAs received from animals or any sources other than humans; 4) Non-English articles; 5) Studies containing insufficient data for comparisons; 6) Any article in which the patient's selection intersects with another article.

Data extraction

We searched the databases separately and collected the following data from the qualified studies: first author, country, year of publication, microRNA profiling, study type, time of sampling, expression level, type of specimen, sample size for both controls and pregnancies with PE, type of PE (EOPE, LOPE), test method, gestational weeks at sampling, internal reference, and diagnostic value (sensitivity, specificity, true positive, true negative, false positive, false negative, cut-off, and AUC).

Statistical analysis

All analyses were carried out using Comprehensive Meta Analysis V3, MetaDiSc 1.4 and RevMan 5.4 software. We used the $\chi 2$-based (Huang et al. 2016) Cochran's Q test and Higgin' I^2 statistics to determine the degree of heterogeneity among studies. Values with $P < 0.10$ or $I^2 > 50\%$ were considered to have significant heterogeneity, and this was followed by application of the random-effects model. The subgroup analyse and threshold effect were used to identify probable sources of heterogeneity (Yin et al. 2020). In addition, we used funnel plot to test the chances of publication bias cross studies, results with $P<0.10$ indicated to the presence of statistical publication bias.

Results

Literature selection

We searched 413 records in PubMed, EMBASE, web of science, and the Cochrane Library. Of these, 172 duplicate studies were excluded. We excluded 195 records after reading the titles and abstract, these including 97 (reviews, conference abstracts), 11 irrelevant studies, 37 not about PE, 21 not about miRNAs, 2 non-English studies, and 27 animal studies. Subsequently, we assessed the remaining 46 full-text articles with exclusion of 38 studies based on our exclusion criteria, including 29 without complete data, 5 without suitable comparisons, 4 overlapping data. In total, 8 studies were ultimately included in this study (Altındirek 2021; Dong et al. 2019; Kim et al. 2020; Motawi et al. 2018; Murakami et al. 2018; Timofeeva et al. 2018; Tolba et al. 2020; Whigham et al. 2020). A flowchart of the selection process for this meta-analysis study is presented in (Fig. 1).

Study characteristics

Table 1 summarizes the main studies' characteristics of the final quantitative synthesis. In total, 8 articles (published between February 2017 and June 2021) were added to this meta-analysis study, including in total 704 pregnant women (350 normal pregnancies and 354 PE patients). The sources of microRNAs included are as follows: whole blood, plasma, serum, and plasma exosomes. Additionally, some studies did not distinguish between the types of PE. qRT-PCR was used in all studies as the primary detection method, with GAPDH, RNU6-2, SNORD-95, Cel-miRNA-39, SNORD44, SNORD48, U6, RNU6-B, and miR191as internal controls.

Quality assessment

A methodical quality assessment against QUADAS2 criteria is presented in (Fig. 2). The poor design of some case-control studies was a key constraint of this quality assessment, although generally the quality was acceptable.

Threshold effect

We used the MetaDisc 1.4 for threshold- analysis, A Spearman correlation coefficient (r) between the logit of TPR and logit of FPR (1-specificity) was calculated, threshold effect is suggested by a strong positive correlation r with a value less than 0.05, in our meta-analysis Spearman-correlation coefficient were 0.451 (p-value = 0.070) indicating no threshold effect exist in the meta-analysis.

Diagnostic efficiency of circulating microRNAs in PE patients

There was a significant heterogeneity among the studies, therefore the random-effects model was used in this

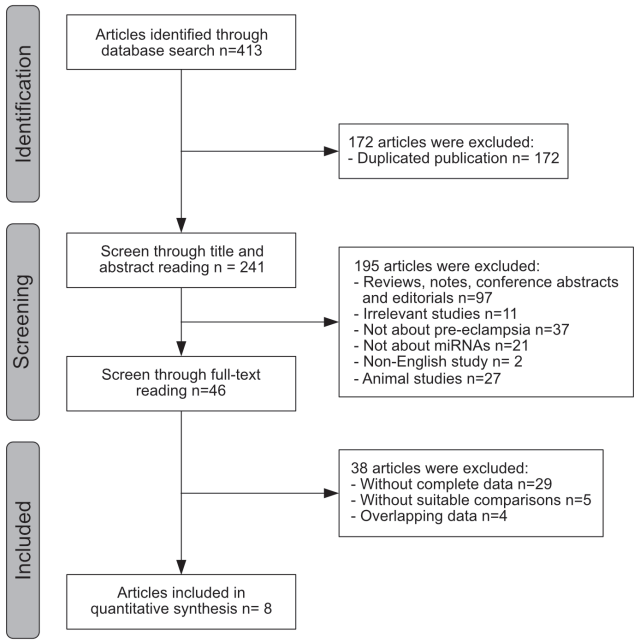

Figure 1. The flow chart of literature selection according to PRISMA guideline.

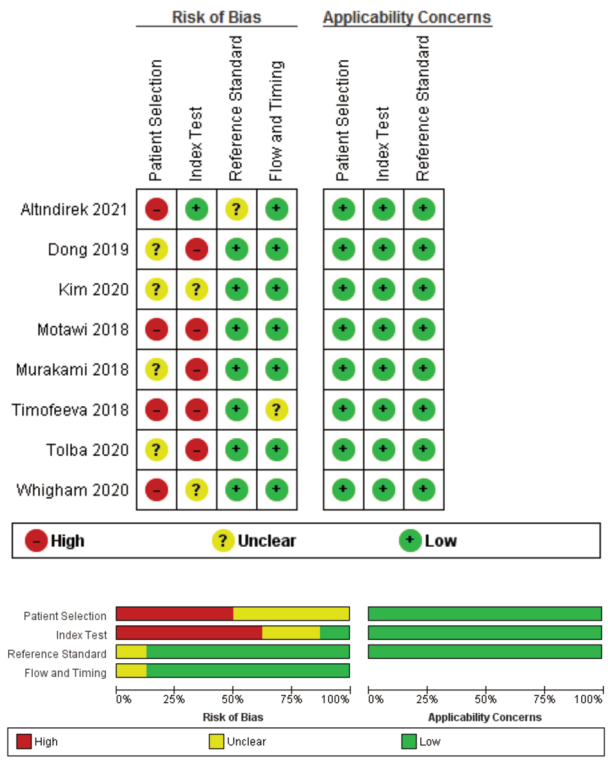

Figure 2. Evaluation of risk of bias by (QUADAS-2) tool. (A) Risk of bias summary and (B) risk of bias graph.

Table 1. characteristics of the included studies in the meta-analysis.

No	First author	Country/Year	Sample size					Specimen	MicroRNAs	TP	FP	FN	TN	Sen%	Spe%	Cut-off	AUC	Time of sampling	Internal reference	Level
			Total	PE	N	Control	N													
1	Altındirek	Turkey/2021	53	EO- PE	31	N	22	Plasma	miR-1183	21	0	10	22	0.677	1.000	NA	0.798	26 and 32 weeks	GAPDH	Elevated
2	Tolba	Egypt/2020	50	Both	30	N	20	Serum	miR-210	27	3	3	17	0.900	0.850	2.03	0.933	30-36 weeks	RNU6-2	Elevated
3	Kim	Korea/2020	184	Both	92	N	92	serum	miR-31-5p	88	7	4	85	0.956	0.923	1.275	0.960	Delivery	SNORD-95	Elevated
									miR-155-5p	82	11	10	81	0.891	0.880	1.365	0.931			Elevated
									miR-214-3p	83	19	9	73	0.902	0.793	1.250	0.924			Elevated
									miR-1290-3p	87	14	5	78	0.946	0.848	0.595	0.957			Decreased
4	Whigham	Australia/2020	54	EO- PE	32	N	22	Whole blood	2 miRNAs	14	2	18	20	0.450	0.900	0.298	0.790	36 weeks	miR191, SNORD44, SNORD48	NA
5	Dong	China/2019	40	EO- PE	20	N	20	Plasma	miR-31	19	6	1	14	0.950	0.700	0.947	0.875	Before treatment	U6	Decreased
			40	LO- PE	20		20		miR-21	13	2	7	18	0.651	0.903	2.309	0.793			Decreased
6	Motawi	Egypt/2018	200	Both	100	N	100	Plasma exosomes	miR-136	95	0	5	100	0.950	1.000	2.550	1.000	20-42 weeks	RNU6B	Elevated
									miR-494	86	5	14	95	0.860	0.950	0.470	0.868			Elevated
									miR-495	90	17	10	83	0.900	0.830	1.287	0.940			Elevated
7	Murakami	Japan/2018	57	Both	13	N	44	Plasma	miR-515-3p	11	3	2	41	0.846	0.932	NA	NA	Third trimester	U6	Elevated
									miR-517a	11	11	2	33	0.846	0.750	NA	NA			Elevated
									miR-517c	13	9	0	35	1.000	0.795	NA	NA			Elevated
									miR-518b	13	11	0	33	1.000	0.750	NA	NA			Elevated
8	Timofeeva	Russia/2018	26	EO- PE	16	N	10	Plasma	miR-423-5p	14	2	2	8	0.875	0.800	NA	0.844	Delivery	Cel-miR-39	Elevated

All studies were carried out by us qRT-PCR (Quantitative real-time polymerase chain reaction). PE "Pre-eclampsia", LO-PE "Late onset pre-eclampsia" EO-PE "Early onset pre-eclampsia", NA "Not available", Sen "Sensitivity", Spe "Specificity", AUC "Area under curve", DOR "Diagnostic odds ratio", PLR "Positive likelihood ratio", NLR "Negative likelihood ratio", TP "True positive", FP "False positive", FN "False negative", TN "True negative".

Table 2. Subgroup analysis for the diagnosis of PE.

Subgroup		Sen (95 % CI)	Spe (95 % CI)	AUC (95 % CI)	DOR (95 % CI)	PLR (95 % CI)	NLR (95 % CI)
Ethnicity							
Asian	10	0.91 [0.88-0.94]	0.84 [0.81-0.87]	0.93	58.45 [34.2-99.8]	5.31 [3.97-7.09]	0.12 [0.07-0.20]
Others	7	0.85 [0.81-0.88]	0.92 [0.89-0.95]	0.94	60.32 [21.75-167.25]	8.99 [4.09-19.75]	0.17 [0.08-0.40]
Specimen types							
Plasma	8	0.83 [0.75-0.89]	0.82 [0.77-0.87]	0.92	35.45 [16.65-75.47]	4.34 [3.14-5.98]	0.21 [0.12-0.37]
others	9	0.89 [0.87-0.91]	0.89 [0.86-0.91]	0.95	70.76 [36.01-139.06]	7.44 [4.98-11.12]	0.12 [0.06-0.25]
Total	17	0.88 [0.86-0.90]	0.87 [0.85-0.89]	0.94	57.54 [35.24-93.94]	6.07 [4.48-8.23]	0.14 [0.08-0.23]

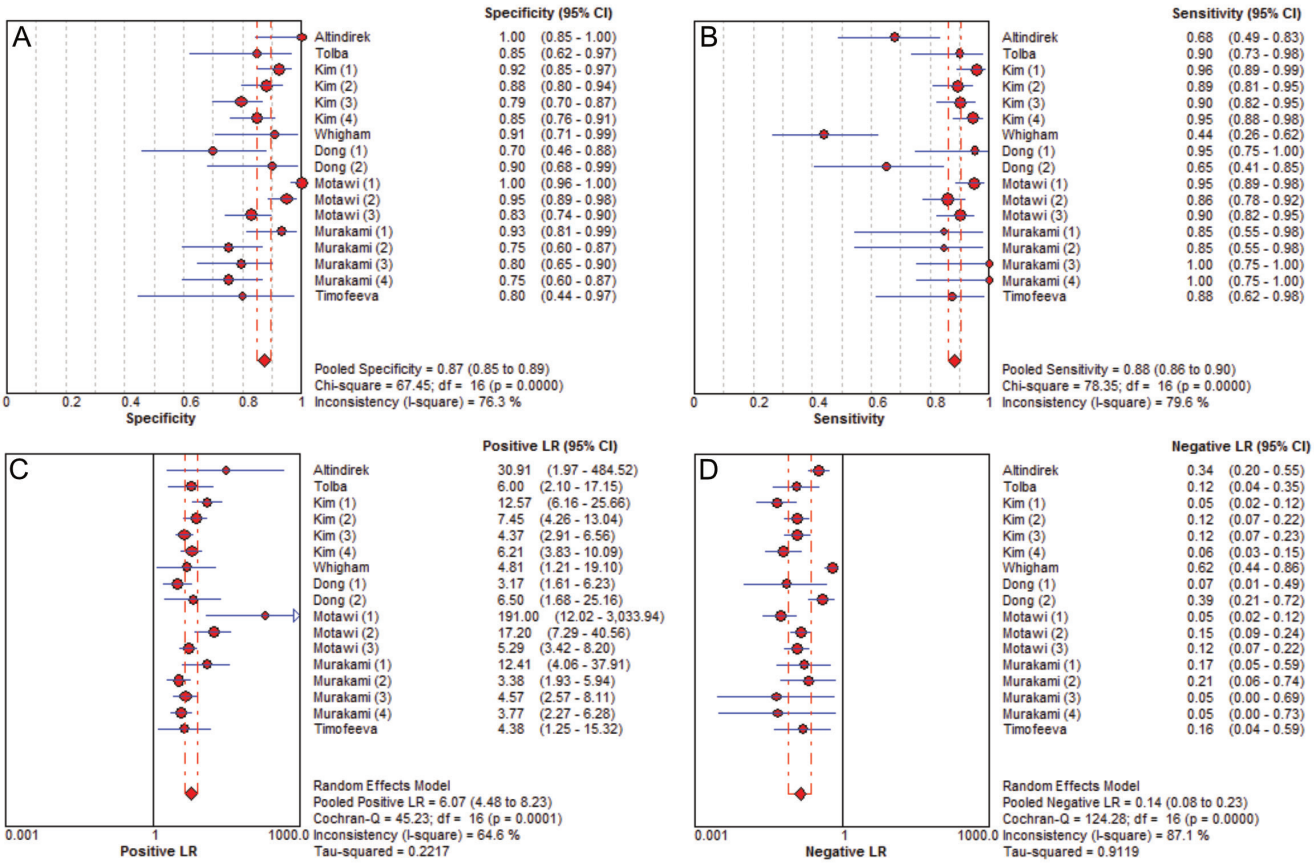

Figure 3. Forest plot of the pooled specificity, sensitivity, positive likelihood ratio, negative likelihood ratio of circulating miRNAs for the diagnosis of PE. (A) Specificity; (B) Sensitivity; (C) PLR; (D) NLR.

meta-analysis (Koushki et al. 2018). By analysing the combined results of some statistical measures of the studies, the results were as follows: specificity 0.87 (95% CI: 0.85-0.89) (Fig. 3a), sensitivity 0.88 (95% CI: 0.86-0.90) (Fig. 3b), positive-likelihood ratio (PLR) 6.07 (95% CI: 4.48-8.23) (Fig. 3c), negative-likelihood ratio (NLR) 0.14 (95% CI: 0.08-0.23) (Fig. 3d), area under curve (AUC) 0.9447 (Fig. 4a), and diagnostic odds ratio (DOR) 57.54 (95% CI: 35.24-93.94) (Fig. 4c). By setting pre-test probability at 20% (Zheng et al. 2019), the Fagan's Nomogram indicated that the post-test probability of positive tests increased to 60% and the post-test probability of negative tests decreased to 3% (Fig. 4b).

Subgroup analysis

We also conducted subgroup analysis, for diagnostic performance, on both ethnicity (Asian or non-Asian), and specimen source (plasma or non-plasma) (Table 2). The findings showed better diagnostic values for non-Asian race than Asians with DOR, 60.32 vs 58.45 and AUC, 0.94 vs 0.93). In parallel, the non-plasma samples showed better diagnostic values than plasma specimen sources with DOR, 70.76 vs 35.45 and AUC 0.95vs 0.92.

Publication bias

We used Comprehensive meta-analysis software (version 3.3.070, USA) to make a funnel plot and Egger's regression test (Koushki et al. 2018). Details are shown in (Fig. 4d). Begg and Mazumdar's test for rank correlation gave a p-value of 0.2016, indicating no evidence of publication bias. Egger's test for a regression intercept gave a p-value of 0.6934, and that means no evidence of publication bias.

Discussion

MicroRNAs has come to the attention of researchers in recent years due to the important role it plays in a variety of diseases. Several studies have proven the role of circulating miRNAs in PE and indicated the possibility of using them as diagnostic biomarkers for PE (Jin et al. 2019; Luque et al. 2014; Wang et al. 2015). Similarly, in malignancies like hepatocellular carcinoma-(HCC) and non-small cell lung cancer-(NSCLC), as well as non-

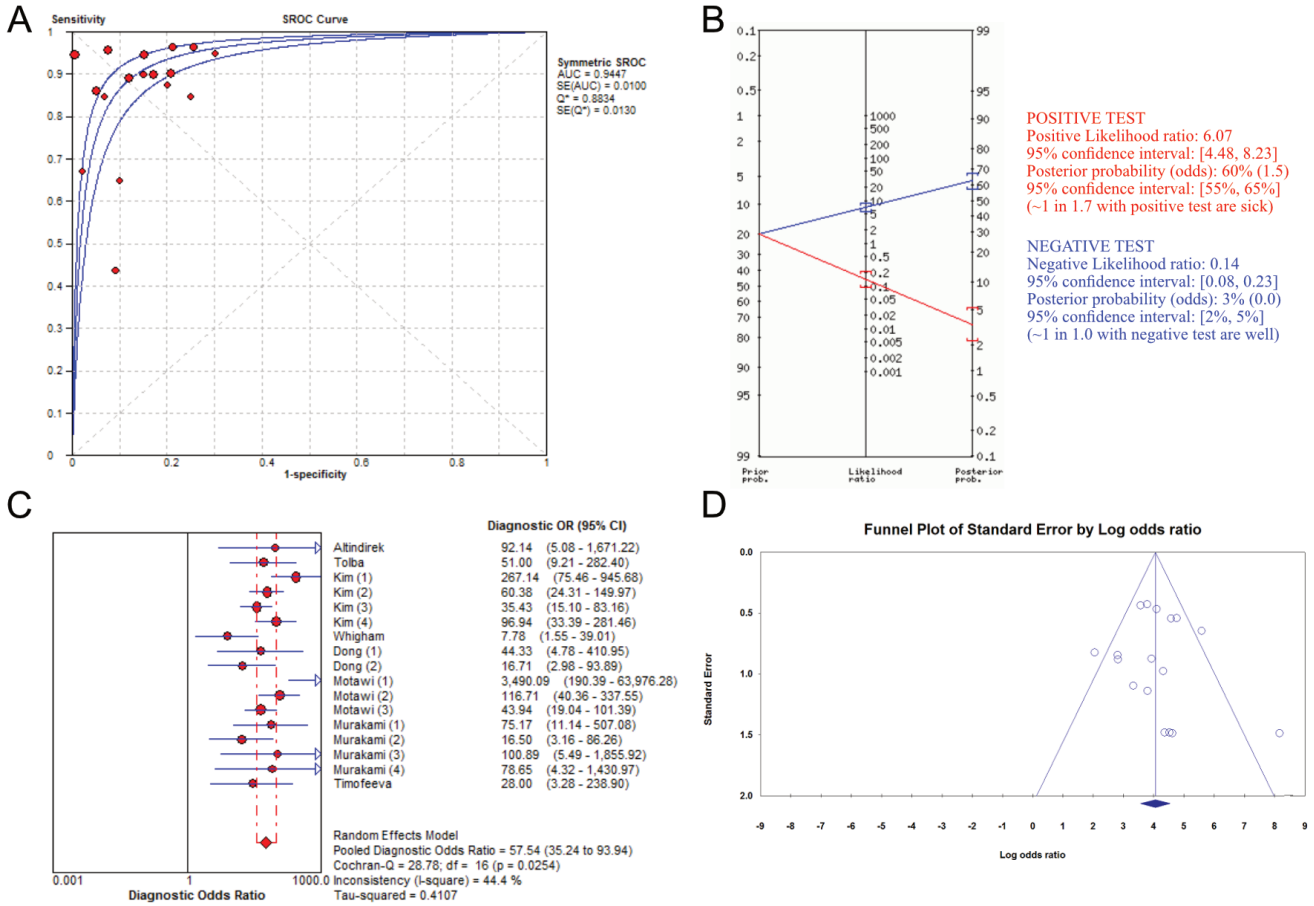

Figure 4. sROC curve, DOR, Fagan's nomogram, and Funnel plot of circulating miRNAs for the diagnosis of PE. (A) sROC curve; (B) Fagan's nomogram; (c) DOR; (D) Funnel plot.

neoplastic illnesses including venous thromboembolism and sepsis, circulating miRNAs plays an important role in early diagnosis of these diseases (Hasegawa et al. 2019; Xiang et al. 2019). As a result of the numerous differences in the results of these studies, we performed a meta-analysis on studies with comparable data for assessing the diagnostic markers.

Principal findings

Our systematic review and meta-analysis study involved 8 articles (17 studies), containing in total 704 pregnant women (350 normal pregnancies and 354 PE patients). In order to find out the diagnostic accuracy we performed the pooled specificity, sensitivity, and the area under the curve (AUC) and they were as follows: 0.88 (95% CI: 0.86-0.90), 0.87 (95% CI: 0.85-0.89), and 0.9447, respectively. Also, the value of diagnostic odds ratio (DOR) showed a high diagnostic efficacy in all the 17 studies. A previous meta-analysis study included 12 studies from 5 articles confirmed our results with pooled sensitivity 0.88 [0.80-0.93], specificity 0.87 [0.78-0.92] and AUC 0.94 (Yin et al. 2020). We also performed LRs tests, LRs correspond nicely to the clinical concepts of (ruling in) and (ruling out) disease (Grimes and Schulz 2005). The more the likelihood ratio for a positive test (LR+, positive likelihood ratio) is greater than 1, the more likely the disease or outcome. The more a likelihood ratio for a negative test (LR-, Negative - likelihood ratio) is less than 1, the less likely the disease or outcome (Deeks and Altman 2004; Johnson 2004; McGee 2002). Our tests showed a pooled LR+ of 6.07 which indicates 6.07-fold increase in the possibility of PE in a pregnant woman with a positive relative to a healthy individual in the diagnostic meta-analysis. Also, the pooled LR- was 0.14 means that the possibility of PE in a pregnant woman, with a negative test, was 14% of that in a healthy individual. Since there was such a significant heterogeneity, we focused on what causes the heterogeneity. After excluding the source of a threshold effect, we conducted a subgroup-analyses for both ethnicity and the specimen source to further inves-

tigate the possible source of heterogeneity. As a result, to the subgroup analysis, we noticed a better diagnostic-value in non-Asian race than Asians with DOR 60.32 [21.75-167.25] vs 58.45 [34.2-99.8] and AUC 0.94 vs 0.93 respectively, also we noticed a better diagnostic-value in non-plasma samples than plasma samples type with DOR 70.76 [36.01-139.06 vs 35.45 [16.65-75.47] and AUC 0.95 vs 0.92, respectively.

Study limitations

In our study we encountered some limitations as follows: Some articles missed cut-off value as well as in some articles PE was not classified by onset time and that could be considered as a source of heterogeneity. Also, regarding internal references, we could not add them to the subgroup analysis due to the lack of suitable data to make a comparison between two groups. Additionally, some studies were conducted on a small sample size, and this may affect the accuracy of results, therefore these results need to be corroborated with other future studies to ensure the validity of the results.

Conclusion

Our meta-analysis shows that circulating microRNAs serve as PE biomarkers due to their high sensitivity and specificity. It also showed that non-plasma samples and non-Asian race may have a higher diagnostic value for PE than the other groups. It is expected that our findings will be useful for future studies related to the microRNA role in diagnosing pre-eclampsia. We suggest further studies with different types of circulating microRNAs for better and broader diagnostic of PE. Furthermore, further research with a larger sample size is needed to explore its function in the pathophysiology of the pre-eclampsia.

Acknowledgment

This study was funded by the Ministry of Science and Higher Education of the Russian Federation N 0852-2020-0028.

References

Abdi F, Aghaie Z, Rahnemaie FS, Alimoradi Z (2018) A systematic review of first trimester biochemical and molecular predictive tests for preeclampsia. Curr Hypertens Rev 14:21-28.

ACOG Committee on Practice Bulletins - Obstetrics (2002) ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 99:159-167.

Altındirek D (2021) Potential diagnostic value of circulating miR-1183 and CHURC1 biomarkers in early-onset preeclampsia. Res Square 1-15.

Bounds KR, Chiasson VL, Pan LJ, Gupta S, Chatterjee P (2017) MicroRNAs: New players in the pathobiology of preeclampsia. Front Cardiovasc Med 4:60.

Deeks JJ, Altman DG (2004) Diagnostic tests 4: likelihood ratios. BMJ 329:168-169.

Dekker G (2002) The partner's role in the etiology of pre-eclampsia. J Reprod Immunol 57:203-215.

Dong K, Zhang X, Ma L, Gao N, Tang H, Jian F, Ma Y (2019) Downregulations of circulating miR-31 and miR-21 are associated with preeclampsia. Pregnancy Hypertens 17:59-63.

Duley L (2009) The global impact of pre-eclampsia and eclampsia. Semin Perinatol 33:130-137.

Gathiram P, Moodley J (2016) Pre-eclampsia: It's pathogenesis and pathophysiolgy. Cardiovasc J Afr 27:71-78.

Grimes DA, Schulz KF (2005) Refining clinical diagnosis with likelihood ratios. Lancet 365:1500-1505.

Hasegawa D, Yamakawa K, Taniguchi K, Murao S, Nishida O (2019) Clinical significance of micrornas in patients with sepsis: Protocol for a systematic review and meta-analysis. Diagnostics 9:211.

Huang QT, Chen JH, Zhong M, Hang LL, Wei SS, Yu YH (2016) Chronic hepatitis b infection is associated with decreased risk of preeclampsia: A meta-analysis of observational studies. Cell Physiol Biochem 38:1860-1868.

Jairajpuri DS, Almawi WY (2016) MicroRNA expression pattern in pre-eclampsia (Review). Mol Med Rep 13:2351-2358.

Jim B, Karumanchi SA (2017) Preeclampsia: pathogenesis, prevention, and long-term complications. Semin Nephrol 37:386-397.

Jin X, Cai C, Qiu Y (2019) Diagnostic value of circulating microRNAs in hepatitis B virus-related hepatocellular carcinoma: A systematic review and meta-analysis. J Cancer 10:4754-4764.

Johnson NP (2004) Advantages to transforming the receiver operating characteristic (ROC) curve into likelihood ratio co-ordinates. Stat Med 23:2257-2266.

Kim S, Park M, Kim JY, Kim T, Hwang JY, Ha KS, Won MH, Ryoo S, Kwon YG, Kim YM (2020) Circulating miRNAs associated with dysregulated vascular and trophoblast function as target-based diagnostic biomarkers for pre-eclampsia. Cells 9:1-18.

Koushki M, Amiri Dash Atan N, Omidi-Ardali H, Rezaei Tavirani M (2018) Assessment of correlation between miR-210 expression and pre-eclampsia risk: a meta-analysis. Rep Biochem Mol Biol 7:94-101.

Li H, Ge Q, Guo L, Lu Z (2013) Maternal plasma miRNAs

expression in preeclamptic pregnancies. BioMed Res Int 2013:970265

Lip SV, Boekschoten MV, Hooiveld GJ, van Pampus MG, Scherjon SA, Plösch T, Faas MM (2020) Early-onset preeclampsia, plasma microRNAs, and endothelial cell function. Am J Obstet Gynecol 222:497.e1-497.e12.

Luque A, Farwati A, Crovetto F, Crispi F, Figueras F, Gratacós E, Aran JM (2014) Usefulness of circulating microRNAs for the prediction of early preeclampsia at first-trimester of pregnancy. Sci Rep 4:4882.

Lv Y, Lu C, Ji X, Miao Z, Long W, Ding H, Lv M (2019) Roles of microRNAs in preeclampsia. J Cell Physiol 234:1052-1061.

McGee S (2002) Simplifying likelihood ratios. J Gen Int Med 17:647-650.

McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, Cohen JF, Deeks JJ, Gatsonis C, Hooft L, Hunt HA, Hyde CJ, Korevaar DA, Leeflang MMG, Macaskill P, Reitsma JB, Rodin R, Rutjes AWS, Salameh JP, Stevens A, Takwoingi Y, Tonelli M, Weeks L, Whiting P, Willis BH (2018) Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies the PRISMA-DTA statement. JAMA - J Am Med Assoc 319:388-396.

Motawi TMk, Sabry D, Maurice NW, Rizk SM (2018) Role of mesenchymal stem cells exosomes derived microRNAs; miR-136, miR-494 and miR-495 in pre-eclampsia diagnosis and evaluation. Arch Biochem Biophys 659:13-21.

Mouillet JF, Chu T, Sadovsky Y (2011) Expression patterns of placental microRNAs. Birth Defects Res Clin Mol Teratol 91:737-743.

Munaut C, Tebache L, Blacher S, Noël A, Nisolle M, Chantraine F (2016) Dysregulated circulating miRNAs in preeclampsia. Biomed Rep 5:686-692.

Murakami Y, Miura K, Sato S, Higashijima A, Hasegawa Y, Miura S, Yoshiura KI, Masuzaki H (2018) Reference values for circulating pregnancy-associated microRNAs in maternal plasma and their clinical usefulness in uncomplicated pregnancy and hypertensive disorder of pregnancy. J Obst Gynaecol Res 44:840-851.

Murphy MSQ, Tayade C, Smith GN (2017) Maternal circulating microRNAs and Pre-eclampsia: challenges for diagnostic potential. Mol Diagn Ther 21:23-30.

Murphy MSQ, Casselman RC, Tayade C, Smith GN (2015) Differential expression of plasma microRNA in preeclamptic patients at delivery and 1 year postpartum. Am J Obstet Gynecol 213:367.e1-367.e9.

Nankali A, Malek-Khosravi S, Zangeneh M, Rezaei M, Hemati Z, Kohzadi M (2013) Maternal complications associated with severe preeclampsia. J Obstet Gynecol India 63:112-115.

Spence T, Allsopp PJ, Yeates AJ, Mulhern MS, Strain JJ, McSorley EM (2021) Maternal serum cytokine concentrations in healthy pregnancy and preeclampsia. J Pregnancy 2021:6649608.

Timofeeva AV, Gusar VA, Kan NE, Prozorovskaya KN, Karapetyan AO, Bayev OR, Chagovets VV, Kliver SF, Iakovishina DY, Frankevich VE, Sukhikh GT (2018) Identification of potential early biomarkers of preeclampsia. Placenta 61:61-71.

Tolba F, Agha A, Rachwan M, Sakr B, Abdella M, Abdelrahman A (2020) Evaluation of microRNA-210(miR-210) as a diagnostic and prognostic biomarker in pre-eclampsia pregnancies. Benha Med J 38:79-93.

Vashukova ES, Glotov AS, Baranov VS (2020) MicroRNAs associated with preeclampsia. Russ J Genet 56:5-20.

Wang H, Wu S, Zhao L, Zhao J, Liu J, Wang Z (2015) Clinical use of microRNAs as potential non-invasive biomarkers for detecting non-small cell lung cancer: A meta-analysis. Respirol 20:56-65.

Wheeler L, Jones MB (1981) Pregnancy induced hypertension. JOGNNurs 10:212-232.

Whigham CA, MacDonald TM, Walker SP, Hiscock R, Hannan NJ, Pritchard N, Cannon P, Nguyen TV, Miranda M, Tong S, Kaitu'u-Lino TJ (2020) MicroRNAs 363 and 149 are differentially expressed in the maternal circulation preceding a diagnosis of preeclampsia. Sci Rep 10:18077.

Wu Y, Li Q, Zhang R, Dai X, Chen W, Xing D (2021) Circulating microRNAs: biomarkers of disease. Clin Chim Acta 516:46-54.

Xiang Q, Zhang HX, Wang Z, Liu ZY, Xie QF, Hu K, Zhang Z, Mu GY, Ma LY, Jiang J, Cui YM (2019) The predictive value of circulating microRNAs for venous thromboembolism diagnosis: A systematic review and diagnostic meta-analysis. Thromb Res 181:127-134.

Yin Y, Liu M, Yu H, Zhang J, Zhou R (2020) Circulating microRNAs as biomarkers for diagnosis and prediction of preeclampsia: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 253:121-132.

Zheng WF, Zhan J, Chen A, Ma H, Yang H, Maharjan R (2019) Diagnostic value of neutrophil-lymphocyte ratio in preeclampsia: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 98:e18496.