Review Article

Analysis of Varying MicroRNAs as a Novel Biomarker for Early Diagnosis of Preeclampsia: A Scoping Systematic Review of the Observational Study

Abstract

Background: Preeclampsia (PE) is a pregnancy-related syndrome with moderate mortality. Early diagnosis of the condition remains difficult, with the current diagnostic modalities being ineffective. The varying microRNAs (miRNAs) as a novel biomarker pose an alternative solution with their potential to be reviewed. **Methods:** This study follows the Preferred Reporting Item for Systematic Review and Meta-Analysis Extended for Scoping Review (PRISMA-ScR). PubMed/MEDLINE, CENTRAL/Cochrane, ProQuest, Science Direct, and Wiley Online Library were used for this review. We only include observational studies. A critical appraisal was assessed in this study using QUADAS-2. **Results:** We retrieved 30 observational studies fulfilling the set criteria. Data extracted were synthesized qualitatively based on miRNAs that are more prominent and their area-under-the-curve (AUC) values. In total, 109 distinct dysregulated miRNAs were identified in comparison to healthy controls, with 10 of them (mir-518b, mirR-155, mirR-155-5p, miR-122-5p, miR-517-5p, miR-520a-5p, miR-525-5p, miR-320a, miR-210, and miR-210-3p) being identified in two or more studies. A brief look at the results shows that 49 miRNAs are downregulated and 74 miRNAs are upregulated, though the fold change of the dysregulation in all studies is not available due to some studies opting for a visual representation of the differences using whisker plots, bar charts, and heat map diagrams to visualize the difference from the reference control. **Conclusions:** This study has analyzed the potential of varying miRNAs as potential diagnostic biomarkers and how they might be used in the future. Despite this, potent miRNAs identified should be more emphasized in future research to determine their applicability and connection with the pathogenesis.

Keywords: *Biomarkers, early diagnosis, microRNAs, preeclampsia, pregnancy*

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Introduction

Preeclampsia (PE) is a pregnancy-related syndrome with a prevalence of 5–8% in the world.[1] PE is characterized by high blood pressure and proteinuria, which leads to various pathological processes as a major cause of maternal, fetal, and neonatal mortality and morbidity. Each year, about 76,000 women and 500,000 infants die from PE. PE has also been associated with an increased risk of diabetes mellitus and cardiovascular complications in the mother and later on in the child.[2]

PE which is classified into early-onset PE (EOPE) and late-onset PE (LOPE) may appear after 20 weeks of gestation.[3] In early-onset PE (EOPE), the clinical symptoms experienced by the mother will appear before 33 gestational weeks, whereas in late-onset PE (LOPE), they appear at and after 34 weeks.[4,5] EOPE itself is responsible for the most maternal and fetal mortality and morbidity rates. The placenta plays an integral role in the development of PE. To explain the occurrence of PE, there are pathophysiological differences between EOPE and LOPE. In EOPE, there is a transformation of the spiral arteries resulting in placental hypoperfusion followed by a decrease in nutrients that will be delivered to the fetus. This will also be a sign of fetal growth restriction (FGR). In contrast to EOPE, in LOPE, there is little or no modification of the spiral arteries, which in some cases causes hyperperfusion of the placenta.[1] The high mortality rate in mothers and infants indicates that preventive measures arising from effective diagnostic tools or treatment for PE patients

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remain sub-optimal.[6] The only cure available is to reduce proinflammatory agents in the maternal cardiovascular system through the delivery of the fetus.[7] Until now, the cause of PE is still not fully understood and several studies have been conducted to investigate it.[8] Therefore, it is necessary to develop (bio)markers that can be used to accurately diagnose PE patients early, even before extensive treatment is needed.

Recently, several studies have focused on identifying molecules named microRNAs (miRNAs). miRNAs are small non-coding ribonucleic acid (RNA) molecules containing approximately 22 nucleotides that regulate biological functions within cells, including apoptosis, cell development, and cell differentiation by binding to specific regions of the 3′-untranslated regions (3′-UTR).[9] Various pieces of research evidence indicate that miRNAs play an important role in the process of placental development as well as pregnancy, which play a pivotal role in the pathophysiology of PE.[6] Empirical findings and comparisons show some differentially expressed miRNAs in comparison to controls or true-normal subjects. A previous study in the meta-analysis found that miRNA biomarkers may be potentially important to PE diagnosis. However, the evidence has limited included studies.[10] Moreover, we need to find varying miRNAs than their included studies retrieved. Following that thought process, this study will investigate the potential and variation of miRNA as a diagnostic biomarker for PE with more extensive evidence than in previous studies and contribute toward the realization of sustainable development goals (SDGs) 3.4,[11] which is to reduce premature mortality from non-communicable diseases (NCDs) through prevention and treatment and promote mental health and well-being.

Methods

Study design

This study was conducted following the Preferred Reporting Item for Systematic Review and Meta-analysis for Scoping Review (PRISMA-ScR) [see **Supplementary File 1**].[11] This study aimed to investigate the potential of miRNA as a diagnostic biomarker for PE.

Search strategy

To obtain the relevant studies, the following keywords were used: “mirna” OR “microRNA” OR “mir-” OR “non coding RNA”) AND (“preeclampsia” OR “Toxemias” OR “pregnancy: Gestosis”), altogether with known synonyms and applying the use of medical subject heading (MeSH) terms where appropriate. The search strategy was carried out in five databases, namely, PubMed/MEDLINE, CENTRAL/Cochrane, ProQuest, Science Direct, and Wiley Online Library for records that were published until August 15, 2021.

Inclusion and exclusion criteria

Throughout the creation of this review, we applied the inclusion criteria as follows: (1) observational study design which includes case controls and cohorts, (2) the population being female patients identified with PE or any other specific classifications of PE, (3) index test measured being the alteration of miRNA identified, (4) controls being healthy pregnant patients, and (5) outcome in terms of the type of miRNA studied accompanied with the alteration identified and fold change if available. The exclusion criteria applied were (1) pieces of literature with irretrievable full text, (2) articles that include reviews, letters, commentaries, and conference abstracts, and (3) studies written in languages other than Bahasa Indonesia or English.

Data collection and study outcome

Three independent reviewers carried out data extraction, with any discrepancies later on adjudicated through consensus together. The details extracted from reviewed studies include: (1) authors and the year of publication, (2) population characteristics which include size, characteristics, and age of the sample, (3) study characteristics including the location and study design, (4) biological source of miRNA used, (5) platform of analysis used, and (6) type of miRNA studied accompanied with its alteration and fold change. Secondary outcomes for studies were also extracted for discussions such as the area under the curve (AUC).

Critical appraisal

A risk of bias (ROB) assessment was conducted based on the Quality Assessment of Diagnostic Accuracy Studies –2 (QUADAS 2).[12] Each study is evaluated based on a number of domains that measures the eligibility of patient selection, index test, reference standard, flow, and timing. Each domain is equipped with 3–4 signaling questions to determine the final score being the low, high, or unclear ROB. The first three domains would also be evaluated for concerns regarding the applicability of the research question. The assessments were performed by all reviewers (EGF and SA), with discrepancies resolved by consensus and adjudicated by a third reviewer (MMAZA).

Results

Search results

Literature searching according to the PRISMA flow diagram [Figure 1] resulted in 6145 studies from 5 different databases. Initial screening based on title and abstract relevancy yielded 41 records for full-text screening. After 5 duplicates were excluded, 36 studies were eligible for full-text screening. Six studies were further excluded due to five having incompatible study designs conducted *in vivo* and one study in Chinese. In total, we had 30 studies that

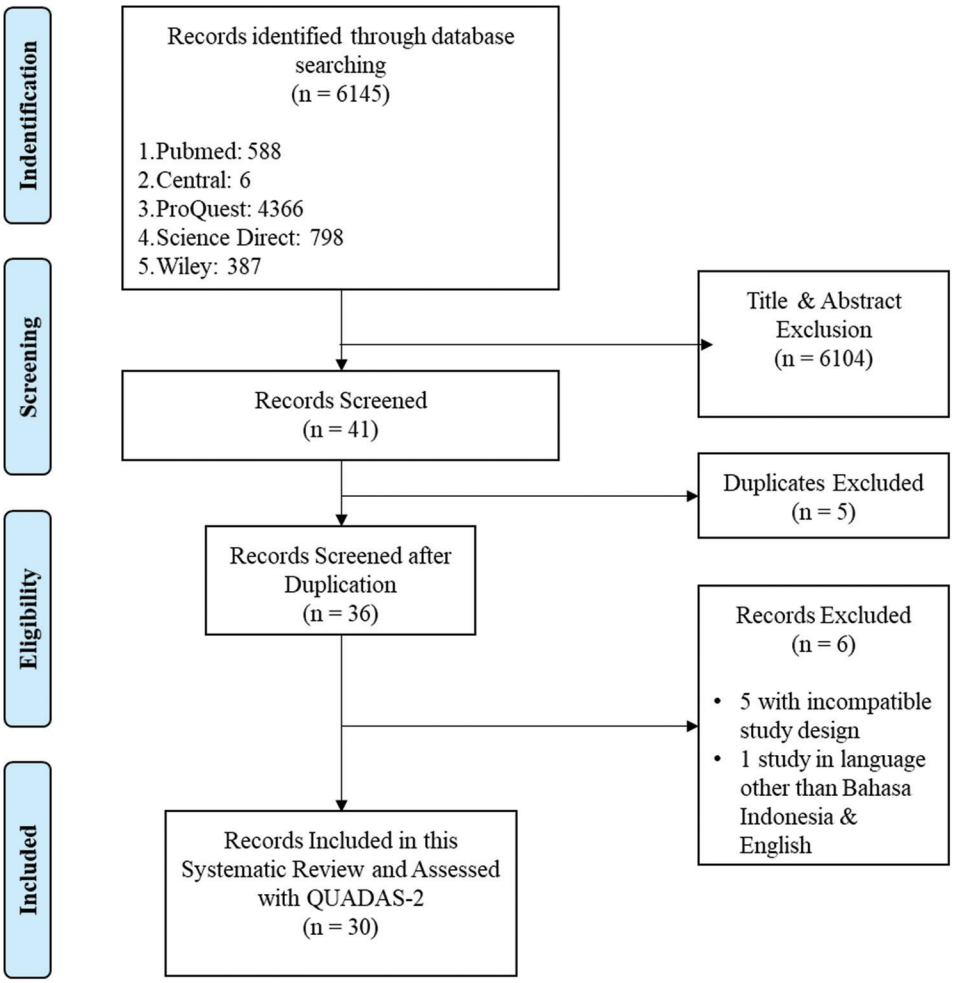

Figure 1: PRISMA flow diagram for literature searching

fulfilled the set criteria and would be further analyzed by tabulation of extracted data for comparison and qualitative synthesis based on the miRNA's dysregulation between patients identified with PE and healthy pregnant females.

Characteristics of the included study

Careful screening by three independent reviewers (MMAZ, EGF, and SA) resulted in 27 case-control[13–39] and 3 cohort studies[40–42] being included in this review. The studies were carried out in mostly affluent countries in Asia, Europe, and the Americas with half of the studies (n = 15) conducted in China. Most of the studies recruited samples ranging from 10 to 40 PE females, accompanied by control groups ranging from 30 to 40 participants, except for a case-control study conducted by Kim *et al.*,[20] which recruited a total of 92 PE patients and an equal number of controls. The mean age of the samples was within the range of 25–46 years [Table 1].

Critical appraisal

Critical appraisal results of the included studies are shown in Figure 2 according to QUADAS-2. Based on the four domains assessing for bias, high and unclear risks of bias are mostly identified in the domain assessing for patient selection. Risks arising from this domain are due to[1] most studies having a case-control study design, and[2] no randomization occurred among the sample group for the index test and reference standard, again due to the nature of the study design. Furthermore, bias was also identified in the flow and timing domain, in which some studies did not include all patients for analysis or did not explicitly state the number of subjects receiving the reference standard. However, the majority (or even all) of the studies show a low ROB for the index test and reference standard used. Moreover, the same could be said for domains that were assessed for their applicability, which all showed a low ROB in terms of concerns relating to the initial research question implemented.

Outcome

In terms of outcome extracted, there were three biological sources for miRNA identified: Plasma (n = 15), placenta (n = 11), and peripheral blood (n = 6) with most of the samples analyzed using quantitative reverse transcription polymerase chain reaction (RT-qPCR) and microarray

Table 1: Characteristics of included studies

Author; Year	Study Design	Location	Sample		
			Size	Characteristics	Age
Dayan; 2017[13]	Case control	Canada, US, Switzerland	30	Women with premature acute coronary syndrome (ACS), aged <55 years, PE (30), and control (146)	46.1 (6.6)
Hromadnikova; 2017[14]	Case control	Netherlands	21	PE (21), IUGR (18), control (58)	34.33 (1.13)
Qian Li; 2015[15]	Case control	China	32	PE (32), control (32)	28.7 (3.6)
Jiang; 2014[16]	Case control	China	20	PE (20), control (20)	28.1 (4.8)
Vashukova; 2016[17]	Case control	Russia	5	PE patients with the onset of proteinuria, PE (5), control (6)	35.0 (2.4)
Zhang; 2020[41]	Cohort	China	30	EOPE (30), control (29)	27.3 (2.1)
Zhong; 2019[19]	Case control	China	3	PE (3), control (3)	26.83 (1.17)
Li (1); 2020[20]	Case Control	China	15	PE (15), control (29)	
Kim; 2020[21]	Case Control	South Korea	92	PE (92), control (92)	32.73 (0.54)
Xie; 2019[22]	Case control	China	57	PE (57), control (57)	27.12 (4.11)
Zhu; 2021[23]	Case control	China	21	PE (21), female with hypertension (13), female healthy (13), control (21)	34.1 (5)
Liu; 2021[24]	Case control	China	30	PE (30), control (30)	41.28 (4.01)
Demirer; 2017[25]	Case control	Turkey	96	Early-onset PE EOPE (*n*=48) and late onset PE LOPE (*n*=48); Healthy control (*n*=52)	EOPE 31 (5.5) LOPE 29.4±5.8 Total PE 30.12±5.7
Jairajpuri; 2017[26]	Cohort	Arab	26	Control (*n*=7) Mild PE (*n*=7) Severe PE (*n*=8)	Control 29 (23-36) Mild PE 30 (25-38) Severe PE 34 (28-39)
Tang; 2019[27]	Case control	China	60	PE (*n*=30) Healthy (*n*=30)	NA
Jelena; 2020[28]	Case control	Serbia	36	PE (*n*=19) Control (*n*=17)	PE 34 (20-51) Control 32 (22-40)
Youssef; 2019[29]	Case control	Egypt	50	PE (*n*=30) Control (*n*=20)	PE 31.77±3.159 Control 29.75±4.241
Niu; 2017[30]	Case control	China	45	PE (*n*=25) Control (*n*=20)	PE (27±2.9) Control (27.9±2.9)
Martinez-Fierro; 2019[31]	Case control	Mexico	16	PE (*n*=16) Control (*n*=18)	PE (23.5±5.1) Control (23.4±5.8)
Timofeeva; 2017[32]	Case control	Russia	54	PE (*n*=28) Control (*n*=26)	27-40
Nejad; 2019[33]	Case control	Iran	40	PE (*n*=20) Controls (*n*=20)	PE (29±1.1) Control (28±0.92)
Dong; 2019[34]	Case control	China	40	EOPE (*n*=20) LOPE (*n*=20)	EOPE (29.10±6.03) LOPE (29.15±5.13)

Contd...

Table 1: Contd...

Author; Year	Study Design	Location	Sample		
			Size	Characteristics	Age
Li (2); 2020[35]	Case control	USA	40	PE (*n*=20) Controls (*n*=20)	PE (28 (25-32)) Control (31 (28-33))
Yoffe: 2018[36]	Case control	Israel	75	PE (*n*=35) Controls (*n*=40)	PE 31.3 (25.9-34.6) Control 29.9 (28.1-34.5)
Awamleh; 2019[37]	Cohort	Canada	79	EOPE (*n*=20) EO-IUGR (*n*=18) EOPE+EO-IUGR (*n*=20) Control (*n*=21)	EOPE (28.6±7.0) EO-IUGR (31.3±5.6) EOPE + EO-IUGR (32.6±5.7) Control (28.2±5.0)
Hromadnikova; 2019[38]	Case control	Czech Republic		PE (*n*=43) Controls1 (*n*=50) Control 2 (*n*=52)	PE (32.34±0.73) Controls 1 (31.88±0.56) Controls 2 (31.21±0.56)
Xueya; 2020[39]	Case control	China	38	PE (*n*=18) Control (*n*=20)	PE (32.5±1.25) Control (32.1±0.75)
Yang; 2019[40]	Case control	China	40	PE (*n*=31) Control (*n*=9)	PE (31.57±2.98) Control (32.83±3.19)
Yuan; 2019[41]	Case control	China	60	PE (*n*=30) Control (*n*=30)	PE: 27.8±2.8 Control: 26.52±4.9
Salomon; 2017[42]	Case control	Chile	45	PE (*n*=13) Control (*n*=32)	PE: 29±1.6 Control: 25±1.2

analysis. In total, there were 109 unique dysregulated miRNAs identified in comparison to the healthy controls, with 10 of them (mir-518b, mirR-155, mirR-155-5p, miR-122-5p, miR-517-5p, miR-520a-5p, miR-525-5p, miR-320a, miR-210, and miR-210-3p) identified in two or more included studies [Table 2]. A brief look at the outcome shows 49 miRNAs being downregulated and 74 miRNAs being upregulated, although fold change of the dysregulation of all studies is not available due to some opting for a visual representation of the differences using whisker plots, bar charts, and heat map diagrams to visualize the difference from the reference control. Other than quantifiable fold change, studies conducted by Hromadnikova (2017) *et al*.,[14] Li[15] *et al*., Timofeeva *et al*.,[30] Jelena *et al*.,[26] Kim *et al*.,[20] Demirer *et al*.,[23] and Hromadnikova (2019) *et al*.[35] further examined the parameters using receiving operative characteristics (ROC) and AUC to determine the overall sensitivity and specificity of the diagnostic biomarker.[14,19,20,23,26,30,35] Studies with the AUC would be evaluated qualitatively separate from the qualitative analysis carried out on the fold change of the miRNA dysregulations. The summary of all included studies can be seen in Table 3 (see supplementary materials),[11] whereas a summary of AUC values is shown in Table 4 and would further be discussed in this review.

Discussion

PE is defined as new-onset gestational hypertension associated with at least one proteinuria, maternal organ dysfunction, or uteroplacental dysfunction in or after 20 weeks of gestation.[43] Additionally, PE may develop either intrapartum or postpartum for the first time. To confirm hypertension, blood pressure has to be measured on two occasions with an appropriate tool.[44] Other diagnosing methods such as detecting proteinuria could also be used for diagnosing PE. The current method and golden standard for diagnosing proteinuria is via a 24-hour urine analysis. However, this method has several disadvantages, such as its time-consuming nature, the requirement of refrigeration, and often incomplete samples.[45] Other laboratories and imaging tests of women with *de novo* hypertension require hemoglobin, platelet count, serum creatinine, liver enzymes, and uric acid serum in determining the presence of any maternal organ dysfunction and the diagnosis of PE. In the pathogenesis of PE, levels of sFlt-1 and lower levels of PlGF are subtle before the onset of the disease.[46] Therefore, screening of these components has shown to have great sensitivity and specificity in diagnosing PE. Trials conducted by Fox *et al*.[47] showed that PIGF screening for PE diagnosis is significantly faster and safer in terms of maternal adverse events and morbid neonatal outcomes. With the difficulties in predicting and diagnosing PE, several studies started to investigate other marker algorithms for predicting PE. These markers employ the same diagnostic capabilities such as identifying dysregulation in (1) A (PAPP-A), (2) disintegrin and metalloproteinase 12 (ADAM12), (3) placental growth factor (PIGF), (4) placental protein 12, (5) angioprotein 1/2, (6) inhibin & activin A, (7) soluble endoglin, (8)

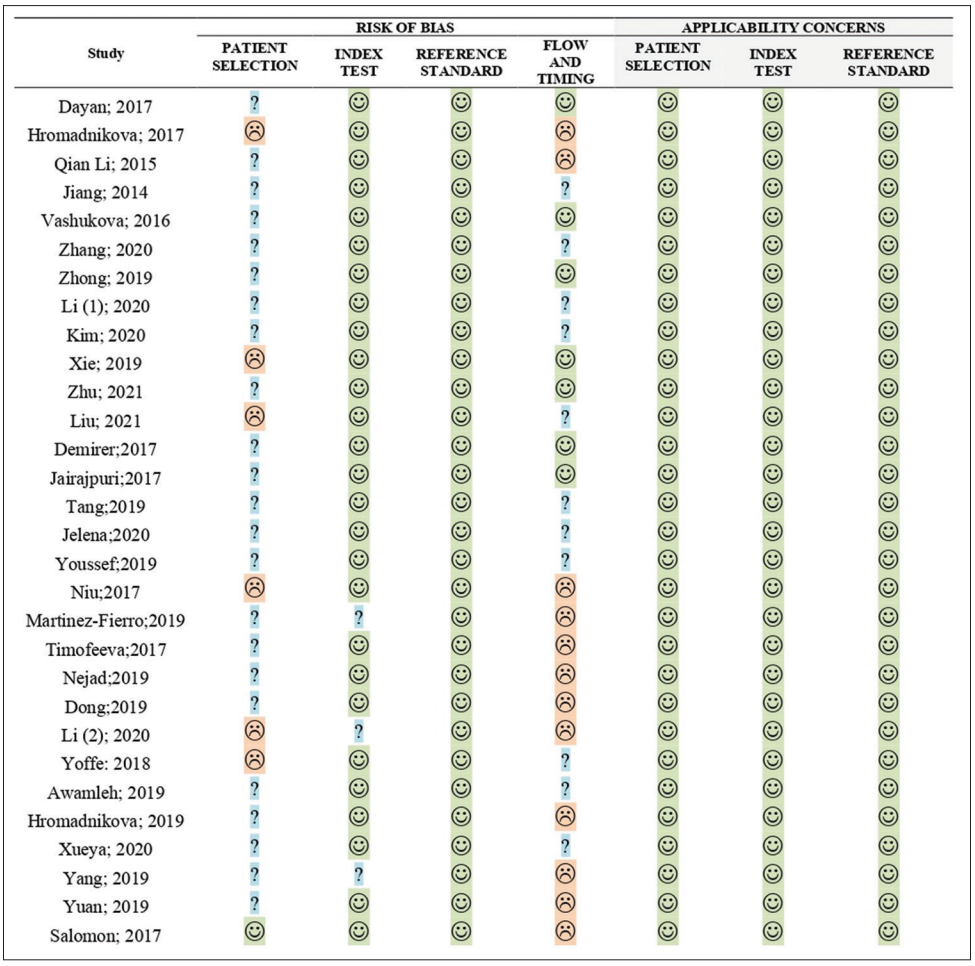

Figure 2: ROB of included studies

soluble fms-like tyrosine kinase 1 (sFLt-1), and (9) human chorionic gonadotropin (hCG).

Despite being repeatedly reviewed, these diagnostic markers are still categorized as insufficient due to the limitation of reliability and validity.[48] Other studies have shown that cffDNA is also dysregulated, thus having the potential as a marker. However, cffDNA usage is again limited because of its low levels after the second trimester, making the biomarker very time-bound in terms of its applicability.[49] Early detection and prediction of PE have been the main focus for prevention, translating the amount of effort being put into early detection tools. Despite these efforts, the sensitivity and predictive value of these markers remain sub-optimal. Therefore, new solutive tools for diagnosing and predicting PE are continuously being sought.

MicroRNAs (miRNAs), are small single-stranded molecules of 22 nucleotides among non-coding RNAs, which are not involved in protein translation and transcription.[50] miRNA is considered a post-transcriptional regulatory molecule with the ability to degrade mRNA and suppress translation.[50] Studies have shown a subtle difference in the expression of miRNA in PE. This pattern of miRNA is detected in the placenta, peripheral blood, mesenchymal stem cells (MCs), umbilical cord blood, and umbilical vein endothelial cells.[8] This indicates the availability of miRNAs or circulating miRNAs in biological sources relevant to PE and the importance of source location which could have a varying

Table 2: miRNAs identified multiple times in included studies

miRNA identified	Times identified	Included studies
mir-518b	3	Hromadnikova, 2017; Demirer, 2017; Jelena 2020
mirR-155	2	Youssef, 2019; Jairajpuri 201
mirR-155-5p	2	Demirer, 2017; Kim, 2020
miR-122-5p	2	Dayan, 2017; Xueya, 2020
miR-517-5p	2	Hromadnikova, 2017; Hromadnikova, 2019
miR-520a-5p	2	Hromadnikova, 2017; Hromadnikova, 2019
miR-525-5p	2	Hromadnikova, 2017; Hromadnikova, 2019
miR-320a	2	Zhong, 2019; Xie, 2019;
miR-210	4	Li, 2015; Vashukova, 2016; Jairajpuri, 2017; Youssef, 2019
miR-210-3p	3	Jelena, 2020; Nejad, 2019

Table 3: Outcomes of included studies

Author; Year	miRNA source	Platform	miRNA studied	miRNA Dysregulation	
				Alteration	Fold Change
Dayan; 2017	Plasma	RT-PCR	miR-126-3p	Downregulated	1.3-2.8
			miR-146a-5p	Downregulated	
			miR-122-5p	Downregulated	
Hromadnikova; 2017	Plasma	RT-PCR	miR-517-5p	Upregulated	NA
			miR-516b-5p	Upregulated	
			miR-518b	Upregulated	
			miR-520a-5p	Upregulated	
			miR-520h	Upregulated	
			miR-525-5p	Upregulated	
Qian Li; 2015	Plasma	RT-qPCR	miR152	Upregulated	NA
			miR183	Upregulated	
			miR210	Upregulated	
Jiang; 2014	Placenta	Microarray, RT-qPCR	miR335	Upregulated	NA
			miR584	Upregulated	
Vashukova; 2016	Placenta	RT-PCR	miR-515-3p	Upregulated	NA
			miR-515-5p	Upregulated	
			miR-518a	Upregulated	
			miR-518e	Upregulated	
			miR-527	Upregulated	
			miR-518c	Upregulated	
			miR-519e	Upregulated	
			miR-524	Upregulated	
			miR-210	Upregulated	
			miR-223	Downregulated	
			let-7f	Downregulated	
			miR-135b	Downregulated	
Zhang; 2020	Placenta	Microarray, RT-qPCR	hsa-miR-937	Downregulated	0.37
			hsa-miR-3907	Downregulated	0.32
			hsa-miR-367*	Upregulated	3.97
Zhong; 2019	Plasma	Microarray, RT-qPCR	hsa-miR-1304-5p	Upregulated	2.10
			hsa-miR-320a	Upregulated	2.25
			hsa-miR-5002-5p	Upregulated	1.63
			hsa-miR-188-3p	Downregulated	0.26
			hsa-miR-211-5p	Downregulated	0.32
			hiv1-miR-TAR-3p	Downregulated	0.33
			hsa-miR-4498	Downregulated	0.40
Li (1); 2020	Plasma	Microarray, RT-qPCR	miR-125b	Upregulated	3.86
Kim; 2020	Plasma	Microarray, RT-qPCR	miR-31-5p	Upregulated	NA
			miR-155-5p	Upregulated	
			miR-214-3p	Upregulated	
			miR-1290-3p	Downregulated	
Xie; 2019	Placenta	RT-qPCR	miR-320a	Downregulated	NA
Zhu; 2021	Serum	RT-qPCR	miR-27b-3p	Upregulated	NA
Liu; 2021	Placenta	RT-qPCR	miR-491-5p	Upregulated	NA
Demirer; 2017	Peripheral blood leukocytes	qPCR	miR- 518b	Upregulated	NA
			miR-155-5p	insignificant	
			miR-21-3p	insignificant	
Jairajpuri; 2017	Plasma	RT-PCR Microarray	miR- 215	Upregulated	7.9
			miR-155	Upregulated	6.8
			miR-650	Upregulated	6.2
			miR-210	Upregulated	5.7
			miR-21	Upregulated	5.0
			miR-18a	Downregulated	0.224
			miR-19b1	Downregulated	0.188
Tang; 2019	Placenta	RT-qPCR	miR-424	Downregulated	NA

Contd...

Table 3: Contd...

Author; Year	miRNA source	Platform	miRNA studied	miRNA Dysregulation	
				Alteration	Fold Change
Jelena; 2020	Plasma	dd-PCR	miR518b	Upregulated	NA
			miR210-3p	Insignificant	
Youssef; 2019	Placenta	RT-qPCR	miR-210	Upregulated	>2
			miR-155	Upregulated	
Niu; 2017	Placenta	Functional assay	miR-30a-3p	Upregulated	2.361±0.85
Martinez-Fierro; 2019	Plasma	RT-qPCR	hsa-miR-628-3p	Downregulated	12≥3
			hsa-miR-628-5p	Upregulated	
Timofeeva; 2017	Plasma, placenta	RT-PCR	Placenta		>2
			miR-532-5p	Downregulated	
			miR-423-5p	Downregulated	
			miR-127-3p	Downregulated	
			miR-539-5p	Downregulated	
			miR-629-5p	Downregulated	
			miR-519a-3p	Downregulated	
			miR-7c-5p	Downregulated	
			Plasma		
			miR-423-5p	Upregulated	
			miR-519a-3p	Upregulated	
			let-7c-5p	Upregulated	
Nejad; 2019	Plasma	RT-PCR	miR-210-3p	Upregulated	33±0.46
			miR-517c-3p	Upregulated	33.7±0.42
Dong; 2019	Plasma	RT-qPCR	miR-31	EOPE	EOPE
			miR-21	Downregulated	1.03±0.78
			miR-16	Upregulated	0.61±0.42
				Upregulated	1.21±0.66
Li (2); 2020	Plasma	RT-qPCR	miR-153-3p	Downregulated	NA
			miR-222-3p	Upregulated	
			miR-224-5p	Upregulated	
			miR-325	Downregulated	
			miR-342-3p	Downregulated	
			miR-532-5p	Upregulated	
			miR-653-5p	Downregulated	
Yoffe: 2018	Plasma	RT-qPCR	miR-182	Downregulated	0.54
			miR-10b	Downregulated	0.50
			miR-25	Downregulated	0.61
			miR-4433b	Upregulated	1.71
			miR-99b	Downregulated	0.65
			miR-143	Downregulated	0.62
			miR-151a	Downregulated	0.75
			miR-191	Downregulated	0.75
			miR-146b	Downregulated	0.75
			miR-221	Upregulated	1.44
			miR-let-7g	Upregulated	1.27
			miR-486	Downregulated	0.70
Awamleh; 2019	Placenta	RT-qPCR	miR-193b-3p	Upregulated	NA
			miR-193b-5p	Upregulated	
			miR-210-3p	Upregulated	
			miR-3651/b-3p	Upregulated	
			miR-520a-3p	Upregulated	
			miR-210-5p	Upregulated	
			miR-181a-2-3p	Upregulated	
			miR-33b-3p	Upregulated	
Hromadnikova; 2019	Peripheral blood	RT-qPCR	miR-517-5p	Downregulated	NA
			miR-520a-5p	Downregulated	
			miR-525-5p	Downregulated	

Contd...

Table 3: Contd...

Author; Year	miRNA source	Platform	miRNA studied	miRNA Dysregulation	
				Alteration	Fold Change
Xueya; 2020	Peripheral blood	RT-qPCR	miR-3130-3p	Upregulated	NA
			miR-371b-3p	Upregulated	
			mir-656-3p	Upregulated	
			mir-877-5p	Upregulated	
			miR-196b-5p	Upregulated	
			miR-518a-5p	Upregulated	
			miR-151b	Upregulated	
			miR-125a-5p	Upregulated	
			miR-3903	Upregulated	
			miR-122-5p	Downregulated	
			miR-182-5p	Downregulated	
			miR-3620-5p	Downregulated	
			miR-363-5p	Downregulated	
			miR-576-3p	Downregulated	
Yang; 2019	Peripheral blood and plasma	RT-qPCR	miR-411	Downregulated	0.34
			miR-376c	Downregulated	0.44
Yuan; 2019	Placenta	RT-qPCR	miR-16	Upregulated	NA
Salomon; 2017	Peripheral blood	RT-qPCR	miR-486-1-5p	Upregulated	NA
			miR-486-2-5p	Upregulated	

MicroRNA (miRNA), preeclampsia (PE), quantitative reverse transcription polymerase chain reaction (RT-qPCR), intrauterine growth restriction (IUGR), early-onset PE (EOPE), late-onset PE (LOPE)

Table 4: Summary of studies with AUC included

Sources	microRNA	Dysregulation	AUC	Reference
Plasma	miR-517-5p	Upregulated	0.7	Hromadnikova; 2017
	miR-516b-5p	Upregulated	0.608	
	miR-518b	Upregulated	0.55	
	miR-520a-5p	Upregulated	0.495	
	miR-520h	Upregulated	0.451	
	miR-525-5p	Upregulated	0.475	
	miR-152	Upregulated	0.94	Li (1); 2015
	miR-183	Upregulated	0.97	
	miR-210	Upregulated	0.93	
	miR-125b	Upregulated	0.763	Li (2); 2020
	miR-423-5p	Upregulated	0.844	Timofeeva; 2017
	miR-518-b	Upregulated	0.175	Jelena; 2020
	miR-31-5p	Upregulated	0.96	Kim; 2020
	miR-155-5p	Upregulated	0.93	
	miR-214-3p	Upregulated	0.924	
	miR-2190-3p	Downregulated	0.957	
Peripheral Blood	miR-518b	Upregulated	0.65	Demirer; 2017
	miR-517-5p	Downregulated	0.812	Hromadnikova; 2019
	miR-520a-5p	Downregulated	0.806	
	miR-525-5p	Downregulated	0.802	

correlation with expression profiles, either upregulated or downregulated. In PE, altered miRNA expression may indicate the severity and its involvement in metabolic changes and other essential mechanisms.[51–53] However, the definite difference (between women with PE and healthy pregnant women) is in the regulation of trophoblast function, angiogenesis, and mesenchymal stem cell function as a predictor for diagnosis. Moreover, the detection of nucleic acid molecules is proven to be essential and even necessary to screen for congenital abnormalities such as PE.

As mentioned before, from the 109 dysregulated miRNAs identified, 10 were reported across 15 studies, thus indicating a higher probable significance in terms of their applicability [Table 2].[13,14,17,18,20,21,23,26,27,31,35,36,42] However, caution should be taken for qualitative synthesis, and numbers alone should be a sole comparator for its significance. This is definitely true for two studies conducted by Hromadnikova *et al*. in 2017 and 2019,[14,35] with the latter identifying the same miRNA sequence in the previous study. Other than times identified, the easiness of a miRNA as a potent biomarker could potentially be identified based on their margin difference.[18,19,41] Based on fold change alone, the analysis could be carried out by identifying the miRNA sequence based on the greatest fold change identified for the respective source [Table 3]. For miRNAs acquired from the plasma of a PE-suspect patient, the highest fold change identified was ±33 × for miR-210-3p and miR-517c-3p from a case-control study conducted by Nejad *et al*.[31] On the contrary, hsa-miR-188-3p was identified with a greater downregulation of 0.26×.[18] Interestingly, only plasma-sourced studies explicitly stated the fold change of the miRNA identified, with an exception of Niu *et al*.'s study[28] which showed an upregulation of 2.36× for miR-30a-3p and Youssef *et al*.'s study[27] with both miR-210 and miR-155 showing upregulation of more than 2×. However, similar to the number of miRNAs identified, fold change should not be taken slowly as a basis of recommendation due to its vague statistical significance. Carrying on from that statement, the authors decided to do another subset analysis on included studies, where AUC is defined and presented for the identified miRNA.

By definition, AUC or area under the ROC curve signifies the aggregate performance measure of the stated classification threshold, or in this context, the specificity and sensitivity of the respective miRNA as a biomarker for PE. Of the 30 included studies, only 8 studies were completed by Hromadnikova *et al*. in 2017 and 2019, Li *et al*.,2015 Li *et al*.,2020 Timofeeva *et al*., Jelena *et al*., Kim *et al*., and Demirer *et al*. [Table 4].[15,19,20,23,26,30,33,35] AUC values close to 1.0 signify a higher aggregation of sensitivity and specificity, thus signifying a better probability score of that respective miRNA to be used as a biomarker.[19,20] Following these terms, miR-31-5p should be identified as the most prospective and consistent miRNA for PE.[20] However, a more interesting analysis could be carried out by combining the AUC values and the consistency the respective miRNA has based on the number of times the miRNA has been identified across the included studies.

Cross-analysis of both parameters yielded miR-210 (and miR-210-3p), miR-525-5p, and miR-518b.[14,15,17,23,26,27,35,42] Despite the limited literature, both miR-525-5p and miR-518b have a direct association with PE; miR-210 (forward: 5′CUGUGCGUGUGACAGCGGCUGA-3′ and reverse: 5′ AGCCGCUGUCACACGCACAGUU-3′) has frequently been reported to show association with the pathogenesis of PE. This association was further developed within the included studies, in which the overexpression of miR-210 had a significant correlation with urea increase and even higher significance in correlation with systolic, diastolic, mean arterial blood pressure (MAP), and creatine levels of more deteriorated cases of PE on both maternal and fetal parameters. Furthermore, overexpression of miR-210 was also inversely correlated with gestational age and fetal birth weight. Hence, both observations imply how miR-210 could be directly involved in PE and its more severe progressions. However, a conclusion based only on correlation is considerably not clinically feasible; thus, more causative study designs on miR-210 and the other two potential miRNAs should be considered to further coin miRNA for the diagnosis of PE.[15,17,27,42]

However, there are challenges in using miRNA as a diagnostic feature and detecting PE. Some of the challenges are principally associated with the small size, low expression level, and similar sequence among tissue during developmental stage expression.[54] The method in screening studies such as droplet digital PCR, microarrays, quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR), and deep sequencing has their limitation, method, and factor affecting the output of the study.[55] The most common quantification method of miRNA is qRT-PCTR. Therefore, as said before, the lack of different expressions from plasma or serum is concerning. The normalization of controls and methods is variable, impacting the effectiveness of the reaction. However, using different normalization methods in studies leads to inconsistent results. Therefore, a reliable normalization of control and method in each cell, tissue, and condition is demanded.[56] In contrast to the challenges, the implementation of miRNA is related to next-generation sequencing (NGS) in detecting the presence of exosome miRNA in most PE cases. This highly sensitive method of quantifying miRNA expression has been used to detect and identification of novel and altered levels of miRNA.[57] NGS is cost-effective because it is a high ability in capacities. Nevertheless, NGS has some contrary detection because of the low input amount due to extracellular detection.[55] On the overall implementation of detecting PE using miRNA, it can be concluded that miRNA is a potential biomarker and, with the contrast and issues stated before, methodologies and comparisons to *in silico* prediction models are needed for a more precise role of miRNA in broad conditions and suitable biomarkers, especially for PE.

Objectively, this study has its own limitations based on the review methodology and also several factors the included studies possess. Firstly, the large number of dysregulated miRNAs identified may instead signify the inconsistency of actually finding the same miRNA sequence being dysregulated from the sample source. However, provided the robust data of this review, some miRNA sequences have been identified to be dysregulated in multiple studies, even from different sources. Hence, this review would lie on its recommendation potential for the best miRNA used for diagnosis. Furthermore, the sample-to-PE ratio remained consistent throughout all included studies, with most of them tested around the same range. This implies a fairer and equal comparison in terms of the size effect of the included studies. Moreover, all studies included are human-based, thus improving their applicability potential with minor adjustments and testing if needed for public implementation. However, based on the study characteristics, most of the studies were conducted in developed or affluent countries. This however may affect its applicative potential in lower-middle-income countries (LMICs), considering the socio-demographic differences and freely available analysis and diagnostic tools. Moreover, despite being a secondary outcome, the strength and reliability of this review are heavily influenced by AUC values in determining the specificity and sensitivity of the proposed miRNA for diagnosing PE.

Conclusions

The crux of the problem of PE lies in its underlying difficult diagnosis. This study has analyzed the potential of varying miRNAs as potential diagnostic biomarkers and their potential prolonged use in the future. Despite varying sequences of miRNA being identified, some sequences (such as miR-210) that are repeatedly identified for dysregulation should have a higher diagnostic value and, potentially, a higher correlation with the pathogenesis of PE. Potent miRNAs identified should be more emphasized

in future research to determine their applicability and connection with pathogenesis.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary file: 1

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

Section	Item	Prisma-scr checklist item	Reported on page #
Title			
Title	1	Identify the report as a scoping review.	1
Abstract			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	1-2
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	2
Methods			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	2
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	2
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	2
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	2
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	2
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	2
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	2
Results			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	3 and Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	3 and table 1
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	3 and Figure 2
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	3-5, table 2, table 3, and table 4
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	3-5
Discussion			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	5-10
Limitations	20	Discuss the limitations of the scoping review process.	10

Contd...

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Section	Item	Prisma-scr checklist item	Reported on page #
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	10-11
Funding			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	First page

JBI=Joanna Briggs Institute; PRISMA-ScR=Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews. *Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites. †A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote). ‡The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting. § The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, *et al*. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. HYPERLINK "http://annals.org/aim/fullarticle/2700389/prisma-extension-scoping-reviews-prisma-scr-checklist-explanation" doi: 10.7326/M18-0850.