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Blood miRNAs as Potential Diagnostic Biomarkers for Chronic Obstructive Pulmonary Disease: A Meta-Analysis

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Purpose: Investigate the efficacy of blood microRNAs (miRNAs) as diagnostic biomarkers for Chronic Obstructive Pulmonary Disease (COPD).

Patients and Methods: We conducted a comprehensive search in English and Chinese databases, selecting studies based on predetermined criteria. Diagnostic parameters like summarized sensitivity (SSEN), summarized specificity (SSPE), summarized positive likelihood ratio (SPLR), summarized negative likelihood ratio (SNLR), and diagnostic odds ratio (DOR), and area under the curve (AUC) of the summary receiver operating characteristic (SROC) curves were analyzed using a bivariate model. Each parameter was accompanied by a 95% confidence interval (CI).

Results: Eighteen high-quality studies were included. For diagnosing COPD with blood miRNAs, the SSEN was 0.83 (95% CI 0.76–0.89), SSPE 0.76 (95% CI 0.70–0.82), SPLR 3.50 (95% CI 2.66–4.60), SNLR 0.22 (95% CI 0.15–0.33), DOR 15.72 (95% CI 8.58–28.77), and AUC 0.86 (95% CI 0.82–0.88). In acute exacerbations, SSEN was 0.85 (95% CI 0.76–0.91), SSPE 0.80 (95% CI 0.73–0.86), SPLR 4.26 (95% CI 3.05–5.95), SNLR 0.19 (95% CI 0.12–0.30), DOR 22.29 (95% CI 11.47–43.33), and AUC 0.89 (95% CI 0.86–0.91).

Conclusion: Blood miRNAs demonstrate significant accuracy in diagnosing COPD, both in general and during acute exacerbations, suggesting their potential as reliable biomarkers.

Keywords: miRNAs, chronic obstructive pulmonary disease, biomarker, meta-analysis, diagnosis

Background

Chronic obstructive pulmonary disease (COPD) is one of the major respiratory diseases that causes a high economic burden and mortality rates worldwide.[1,2] Epidemiological surveys from around the world show that the incidence rate of COPD has been on the rise, with more than 300 million people worldwide affected by COPD, and an estimated 3.28 million people having died from this disease in 2019, ranking as the third leading cause of death globally.[3] In a large-scale epidemiological survey conducted in China in 2018, the prevalence of COPD among the population aged 40 and above was 13.7%, indicating that COPD is also a serious public health problem in China.[4] Acute exacerbation of COPD (AECOPD) is an important event in the course of COPD, mainly manifested as worsening of respiratory symptoms in the short term, which may be accompanied by fever and other symptoms.[5] Early diagnosis and standardized management may improve quality of life and prognosis for COPD patients, and reduce the risk of AECOPD.[6]

The typical clinical manifestations of COPD patients are chronic cough, sputum production, and difficulty breathing after physical activity. However, some patients may lack corresponding clinical manifestations. Currently in clinical practice, the diagnostic criteria for COPD rely on pulmonary function tests, specifically, a post-bronchodilator FEV1/

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FVC ratio of less than 70%.[1] However, factors like advanced age and disease severity may prevent some patients from undergoing these tests. Therefore, the use of biomarkers that may change in the pathophysiological pathway of this disease may improve the accuracy of future clinical diagnosis and treatment.[7] Blood biomarkers offer a non-invasive, easily accessible diagnostic tool, widely used in clinical practice. For example, testing for long non-coding RNAs in the blood can aid in the initial diagnosis and prognosis of sepsis.[8] In addition, miRNAs in COPD patients' blood have potential as diagnostic biomarkers.[9]

Among various non-coding RNAs, miRNA, a small RNA of approximately 22 nucleotides, plays a pivotal role by binding to the 3' UTR complementary sequence of the mRNA, inducing either degradation or translational inhibition of the target mRNA.[10] In a comprehensive exploration of microarray data from the GEO database, Zhu et al identified differentially expressed miRNAs between COPD and normal human plasma, suggesting a regulatory role for miRNAs in key genes associated with COPD.[11] Wang et al's case-control study highlighted the significance of plasma miR-126 expression in COPD, revealing its potential as a distinguishing biomarker not only between COPD patients and healthy controls but also between AECOPD and stable COPD (SCOPD) patients.[12] With the continual advancement of sequencing technology, the growing body of research on miRNA for COPD diagnosis prompted our meta-analysis to systematically integrate and analyze findings from multiple independent studies, aiming to derive more comprehensive and reliable conclusions regarding the utility of miRNA in COPD diagnosis.

Methods

Literature Search

This study involves the collection and analysis of pre-existing data and publicly available files. The search encompasses databases such as China National Knowledge Infrastructure, Chinese Biomedical Literature Database, PubMed, Embase, and Web of Science. Two researchers independently conducted searches across these databases from their inception to October 2023, focusing on diagnostic literature related to blood miRNAs for distinguishing COPD patients from healthy controls or those with acute exacerbations (AECOPD) and stable conditions (SCOPD). The language criteria for retrieved literature are limited to Chinese and English. The primary focus of the search is on COPD and miRNA, with relevant Medical Subject Headings obtained from the website (https://www.ncbi.nlm.nih.gov/mesh/?term=). A literature search utilizing Boolean logic was performed to enhance the effectiveness of the search process. This study was registered in PROSPERO (NO. CRD42023492486)

Inclusion and Exclusion Criteria

The inclusion criteria for literature are: (1) subjects diagnosed with COPD or AECOPD through lung function tests, excluding other diseases; (2) a control group comprising healthy individuals; (3) literature that explicitly states the use of blood miRNAs to differentiate COPD from healthy individuals or distinguish between AECOPD and SCOPD; (4) the literature directly presenting diagnostic studies with true positive (TP), false positive (FP), false negative (FN), true negative (TN) values, or providing sensitivity and specificity for estimating TP, FP, TN, and FN. Sensitivity is calculated as Sensitivity=TP/(TP+FN) × 100%, and specificity is calculated as Specificity=TN/(TN+FP) × 100%.

The exclusion criteria for literature are: (1) non-diagnostic original literature, such as reviews, meta-analyses, case reports, conference abstracts, comments, etc.; (2) literature from the same author or related literature repeatedly published in the same research population; (3) animal experiments; (4) literature not in Chinese or English.

Data Extraction and Quality Assessment

Two researchers independently conducted the extraction of pertinent data, with a subsequent verification by a third researcher. The extracted data encompassed details such as the first author, publication year, language, country of publication, sample size, age/gender of both the case and control groups, sample source, miRNA type, detection method, normalizer, and direct extraction or evaluated values of TP, FP, FN, and TN from the articles. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was employed to assess the quality of the included literature.[13] Two researchers autonomously performed quality assessments, and in cases of discordant opinions, a third author was engaged

in discussions to achieve consensus. The QUADAS-2 evaluation primarily involved addressing pivotal questions in four domains: patient selection, index test, reference standard, and flow and timing.[13]

Statistical Analysis

The data analysis was conducted using Rev Man 5.4, Stata 15.1, and Meta-Disc 1.4 software. Meta-Disc 1.4 software assessed the threshold effect using Spearman correlation analysis, where a strong positive correlation indicated the possibility of a threshold effect.[14] If no threshold effect was identified, the data were combined for further analysis. The degree of heterogeneity between studies was evaluated using Cochran's-Q test and Higgins' inconsistency index (I^2) test. A value of I^2 less than 50% was considered indicative of low heterogeneity, while values above 50% indicated significant inter-study heterogeneity. A bivariate model was employed to estimate the combined effect, including summarized sensitivity (SSEN), summarized specificity (SSPE), summarized positive likelihood ratio (SPLR), summarized negative likelihood ratio (SNLR), and diagnostic odds ratio (DOR). The bivariate model, being a special random effects model, considered the correlation between study heterogeneity and the two indicators during pooled value calculations, providing more accurate results compared to a simple pooled model.[15,16] Forest plots and summary receiver operating characteristics (SROC) curves were generated, and the area under the curve (AUC) was calculated to assess diagnostic accuracy. The diagnostic value of blood microRNAs was further visualized using a Fagan nomogram, reflecting diagnostic performance through a priori and posterior probability calculations. Publication bias was explored using Deeks' funnel plot. Sensitivity analysis, including Influence analysis and outlier detection, was performed to test result stability. In cases where significant heterogeneity was identified, single-variable meta-regression analysis and subgroup analysis were employed to explore potential sources of heterogeneity.

Results

Literature Search

The literature search formula employing Boolean logical operators is presented in Supplementary Additional File S1. The inclusion and exclusion process is visually depicted in Figure 1. In the initial search, 2515 articles were identified. Following the removal of 1305 duplicate articles, 1210 articles were retained. Subsequently, a screening of titles and abstracts led to the exclusion of 1026 irrelevant publications. A more in-depth examination of the remaining 184 articles resulted in the exclusion of 168 studies that did not meet the specified inclusion criteria. These criteria involved excluding reviews, in vitro and in vivo experiments, as well as articles with sample sources other than blood or those with unusable data. In conclusion, a total of 16 eligible studies[17–32] were incorporated into the meta-analysis, comprising 8 English-language publications and 8 Chinese-language publications. The publication period of the included studies spans from 2013 to 2023. The meta-analysis encompassed a combined total of 1765 patients diagnosed with COPD and 910 individuals in the healthy control groups. Detailed information regarding the basic characteristics of the included studies is presented in Table 1.

Literature Quality Evaluation

The quality assessment of the included literature was conducted using the QUADAS-2 tool, and the results are depicted in Supplementary Figure 1. Notably, all the included studies exhibited a high quality level. However, it's crucial to note that some studies lacked specific details such as age and gender for the healthy control group, potentially introducing selection bias of unknown magnitude. Furthermore, the absence of explicit cutoff values for blood miRNA utilization in COPD diagnosis in some studies presents a risk of bias in the index test. In summary, patient selection and the index test were the main areas of concern, showing unclear and high risk levels. Conversely, reference standard and flow and timing exhibit low-risk profiles. Despite these considerations, the overall quality of the included literature remains high.

Association Between miRNAs and COPD Diagnosis

We conducted a meta-analysis to further elucidate the utility of blood miRNAs in distinguishing between COPD patients and healthy controls. Eleven articles, comprising a total of 18 studies, were included in the meta-analysis. The Spearman

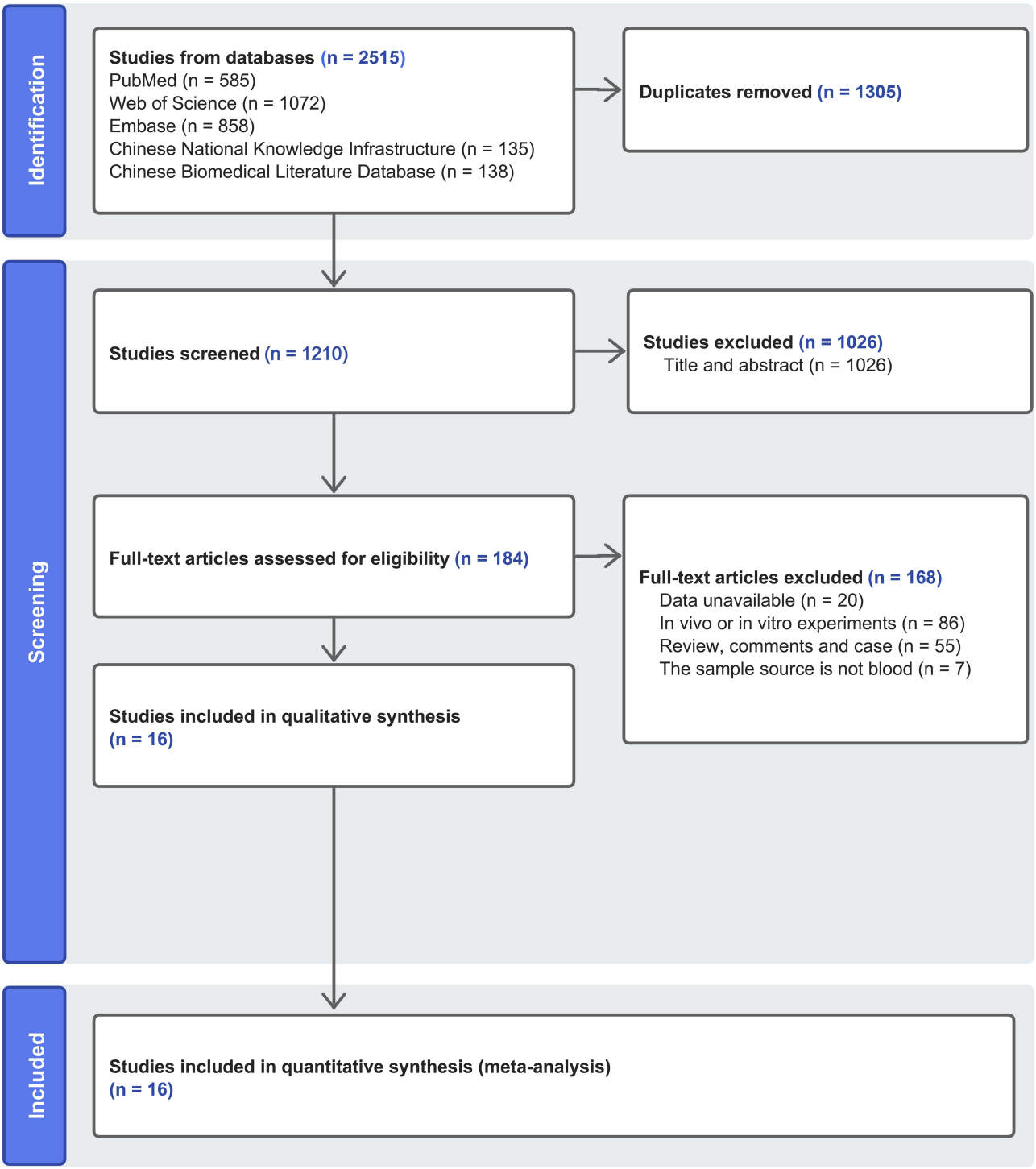

Figure 1 Flow chart for inclusion and exclusion of literature.

correlation coefficient was −0.130, with a p-value of 0.607, indicating no threshold effect. The combined results (depicted in Figure 2a–e) revealed an SSEN of 0.83 (95% CI 0.76–0.89), SSPE of 0.76 (95% CI 0.70–0.82), SPLR of 3.50 (95% CI 2.66–4.60), SNLR of 0.22 (95% CI 0.15–0.33), and DOR of 15.72 (95% CI 8.58–28.77). The AUC was 0.86 (95% CI 0.82–0.88) (Figure 2f). The Fagan's nomogram demonstrated that when blood miRNAs were used to test all individuals with a 50% pretest probability, a positive result increased the posttest probability to 78%, while a negative

Table 1 The Basic Characteristics of the Included Studies

First Author	Year	Country	Language	No. of COPD Patients	Age	Sex (Male/Female)	No. of Control	Age	Sex (Male/Female)	Sample Type	Test Method	Normalizer
Chen et al[17]	2019	China	English	104	SCOPD: 67.53±8.49, AECOPD: 65.13±9.87	88/16	50	63.47±11.31	41/9	Plasma	qRT-PCR	U6
Ding et al[18]	2023	China	English	59	75.12 ± 7.85	50/9	26	71.65 ± 6.35	20/6	Plasma	qRT-PCR	Cel-miR-39-3p
Gao et al[19]	2022	China	Chinese	164	SCOPD: 67.97±8.24, AECOPD: 69.12±7.89	107/57	82	68.27±8.22	57 /25	Plasma	qRT-PCR	U6
Geng et al[20]	2020	China	English	53	60.32± 6.35	32/21	50	59.83±5.29	25/25	Serum	qRT-PCR	U6
Jiang et al[21]	2021	China	Chinese	180	57.84±6.59	104/76	80	58.23±8.34	49/31	Serum	qRT-PCR	U6
Li et al[22]	2022	China	Chinese	262	SCOPD: 62.85±12.08, AECOPD: 64.24±11.03	151/111	110	60.78±10.77	60/50	PBMC	qRT-PCR	U6
Li et al[23]	2023	China	Chinese	100	SCOPD:56.41 ± 6.22, AECOPD: 57.43 ± 6.11	63/37	50	56.86 ± 6.51	30/20	Serum	qRT-PCR	U6
Shen et al[24]	2021	China	English	46	62.3±5.6	36/10	34	61.2±6.3	27/7	Plasma	qRT-PCR	U6
Shi et al[25]	2022	China	English	35	66.89±8.05	24/11	35	66.89±5.86	25/10	Plasma	qRT-PCR	U6
Soeda et al[26]	2013	Japan	English	40	Ex-smoker: 64.6±7.4, Current smoker: 64.7±7.5	36/4	10	62.8±14.6	10/0	Plasma	qRT-PCR	Ath-miR-159
Wang et al[27]	2023	China	English	108	SCOPD:77.1 ± 9.12, AECOPD: 78.4 ± 10.11	88/20	45	75.9 ± 2.66	22/23	Serum	qRT-PCR	U6
Wei et al[28]	2022	China	Chinese	43	SCOPD:57.87 ± 11.12, AECOPD: 70.79 ± 8.08	38/5	26	62.27 ± 7.56	15/11	Blood	qRT-PCR	U6
Zeng et al[29]	2020	China	Chinese	136	65.30 ±10.80	84/52	60	6 4. 2 0 ± 1 0. 5 0	39/21	Plasma	qRT-PCR	U6
Zhao et al[30]	2019	China	Chinese	127	64.05±6.82	78/49	50	NA	NA	PBMC	qRT-PCR	NA
Zhou et al[31]	2021	China	Chinese	205	SCOPD: 67.38±3.80, AECOPD: 67.45±7.62	162/43	101	68.22±6.83	78/23	Serum	qRT-PCR	U6
Li et al[32]	2020	China	English	103	73 (53–85)	79/24	101	60 (50–80)	84/17	Blood	qRT-PCR	U6

Abbreviations: AECOPD, Acute Exacerbations of Chronic Obstructive Pulmonary Disease; COPD, Chronic Obstructive Pulmonary Disease; NA, not available; qRT-PCR, Quantitative Reverse Transcription Polymerase Chain Reaction.

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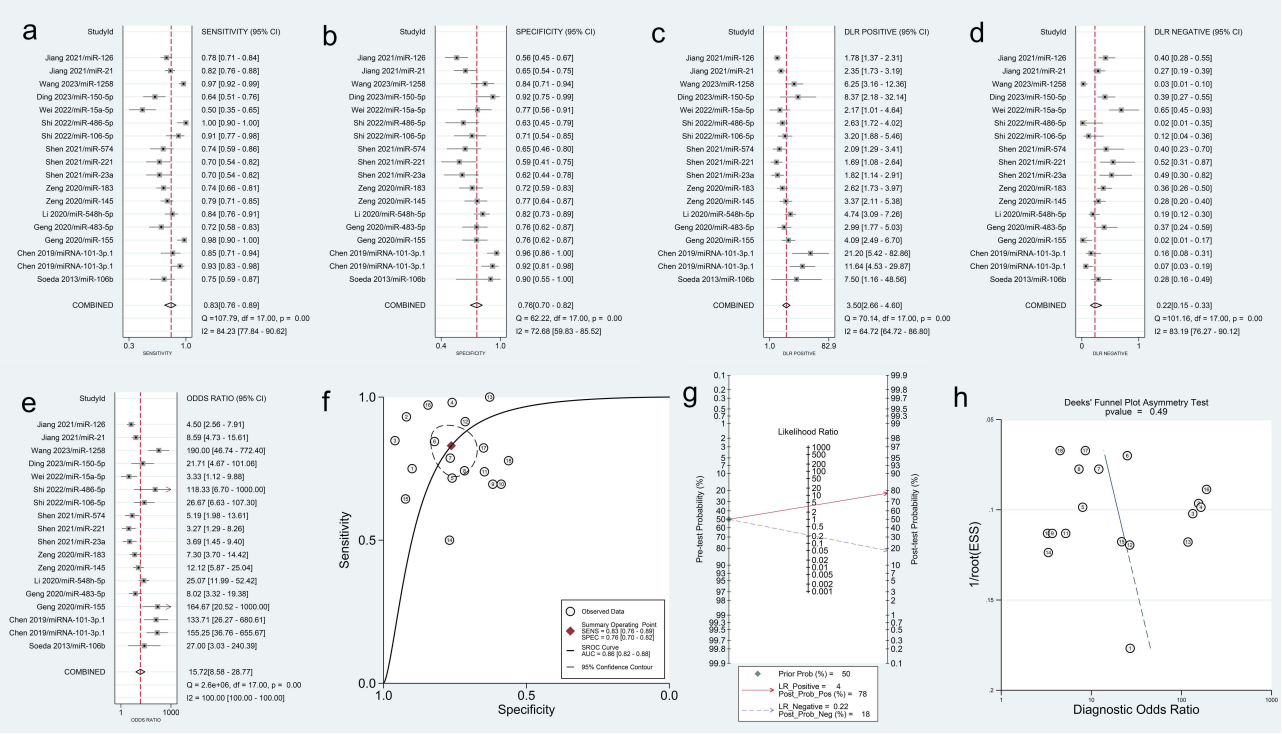

Figure 2 The blood miRNA was utilized to differentiate between COPD patients and the healthy control group in the meta-analysis results. Forest plot of (**a**) SSEN, (**b**) SSPE, (**c**) SPLR, (**d**) SNLR and (**e**) DOR. (**f**) AUC of SROC. (**g**) The fagan's nomogram. (**h**) The results of publication bias.

result decreased the posttest probability to 18% (Figure 2g). The Deek test indicated no publication bias in this meta-analysis (Figure 2h).

Association Between miRNAs and AECOPD Diagnosis

Subsequently, we conducted an additional meta-analysis to further explore the effectiveness of blood miRNAs in differentiating between AECOPD patients and SCOPD controls. Seven articles, encompassing a total of 9 studies, were included in the meta-analysis. The Spearman correlation coefficient was 0.117, with a p-value of 0.764, indicating no threshold effect. The combined results (illustrated in Figure 3a–e) demonstrated an SSEN of 0.85 (95% CI 0.76–0.91), SSPE of 0.80 (95% CI 0.73–0.86), SPLR of 4.26 (95% CI 3.05–5.95), SNLR of 0.19 (95% CI 0.12–0.30), and DOR of 22.29 (95% CI 11.47–43.33). The AUC was 0.89 (95% CI 0.86–0.91) (Figure 3f). The Fagan's nomogram revealed that when blood miRNAs were employed to test all individuals with a 50% pretest probability, a positive result increased the posttest probability to 81%, while a negative result decreased the posttest probability to 16% (Figure 3g). The Deek test indicated no publication bias in this meta-analysis (Figure 3h).

Univariable Meta-Regression and Subgroup Analyses

Due to significant heterogeneity in this study, we conducted Univariable meta-regression and subgroup analyses (Table 2). For the meta-analysis on blood miRNAs in COPD diagnosis, factors such as sample size (>100), English language, sample type (plasma/serum), Normalizer U6, and specific cutoff values were considered. Results suggested that plasma is a potential source of high heterogeneity in SSEN, and whether the sample is plasma or serum is a possible source of high heterogeneity in SSPE (Figure 4a). For the meta-analysis on blood miRNAs in AECOPD diagnosis, focusing on a sample size greater than 100 and all Normalizers being U6, we considered English language, sample type (plasma/serum), and specific cutoff values. The final results indicated that English language is a potential source of high heterogeneity in SSEN, and whether the sample is plasma is a potential source of high heterogeneity in SSPE (Figure 4b).

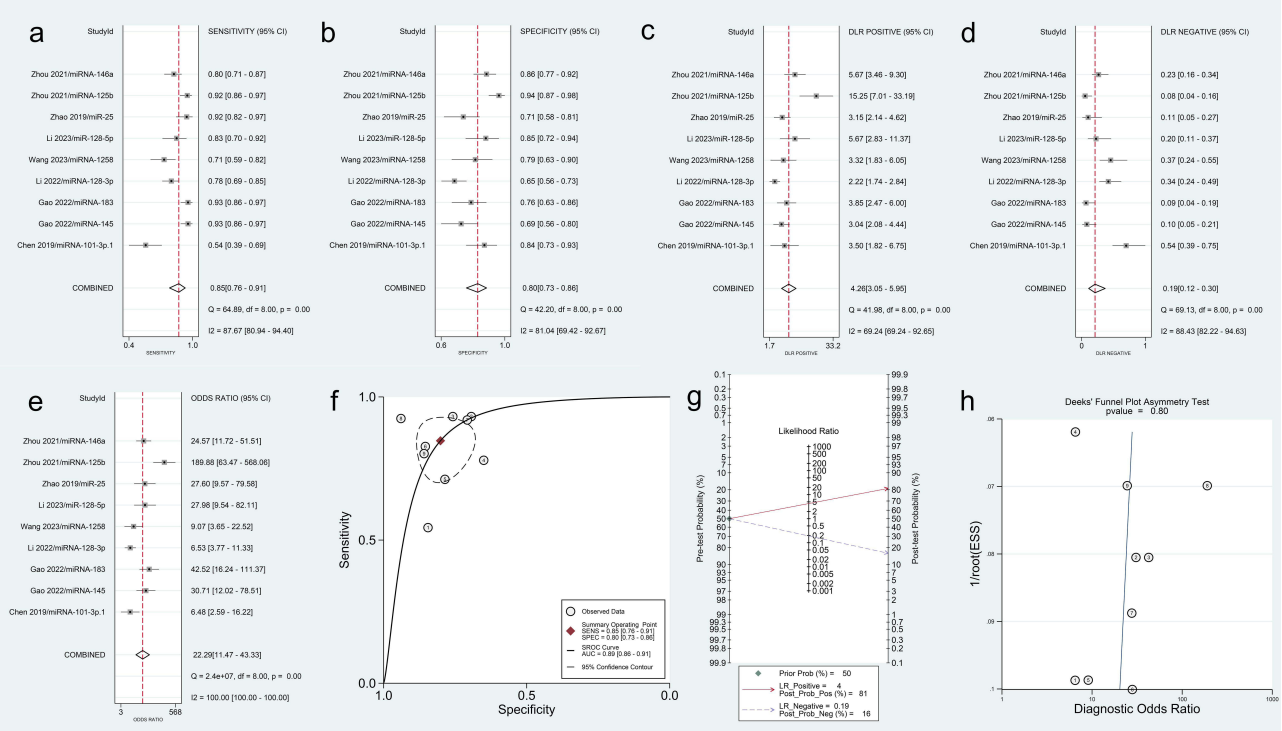

Figure 3 The blood miRNA was utilized to differentiate between AECOPD patients and the SCOPD patients in the meta-analysis results. Forest plot of (**a**) SSEN, (**b**) SSPE, (**c**) SPLR, (**d**) SNLR and (**e**) DOR. (**f**) AUC of SROC. (**g**) The fagan's nomogram. (**h**) The results of publication bias.

Sensitivity Analysis

For the meta-analysis of blood miRNAs used in diagnosing COPD, goodness of fit and bivariate normal analyses (Figure 5a and b) demonstrated that the bivariate model was robustly modeled. Influence analysis identified 3 outliers,

Table 2 Meta Regression and Subgroup Analysis of the Meta-Analysis

	Parameter	Category	No. of Studies	Sensitivity	P value	Specificity	P value
COPD vs Health	Sample>100	Yes	9	0.87 0.80–0.93	0.28	0.77 0.69–0.84	0.02
		No	9	0.78 0.67–0.88		0.76 0.67–0.85	
	English	Yes	13	0.86 0.80–0.92	0.66	0.79 0.73–0.85	0.26
		No	5	0.74 0.60–0.89		0.69 0.58–0.81	
	U6	Yes	16	0.84 0.78–0.90	0.69	0.75 0.69–0.81	0.03
		No	2	0.70 0.44–0.96		0.92 0.82–1.00	
	Plasma	Yes	11	0.82 0.73–0.90	0.03	0.78 0.70–0.85	0.05
		No	7	0.85 0.75–0.94		0.74 0.65–0.84	
	Serum	Yes	5	0.89 0.81–0.97	0.42	0.72 0.61–0.83	0.01
		No	13	0.80 0.72–0.88		0.78 0.71–0.84	
	Cut-off value	Yes	14	0.86 0.80–0.91	0.93	0.78 0.72–0.84	0.35
		No	4	0.70 0.52–0.87		0.70 0.56–0.84	
AECOPD vs SCOPD	English	Yes	2	0.64 0.47–0.81	<0.01	0.82 0.69–0.95	0.26
		No	7	0.88 0.84–0.93		0.80 0.72–0.87	
	Plasma	Yes	3	0.86 0.74–0.97	0.30	0.77 0.65–0.89	0.03
		No	6	0.84 0.75–0.93		0.81 0.74–0.89	
	Serum	Yes	4	0.83 0.72–0.94	0.10	0.87 0.82–0.92	0.12
		No	5	0.86 0.77–0.95		0.73 0.66–0.79	
	Cut-off value	Yes	8	0.84 0.76–0.91	0.26	0.81 0.75–0.88	1
		No	1	0.92 0.80–1.00		0.71 0.48–0.94	

Abbreviations: AECOPD, Acute Exacerbations of Chronic Obstructive Pulmonary Disease; COPD, Chronic Obstructive Pulmonary Disease.

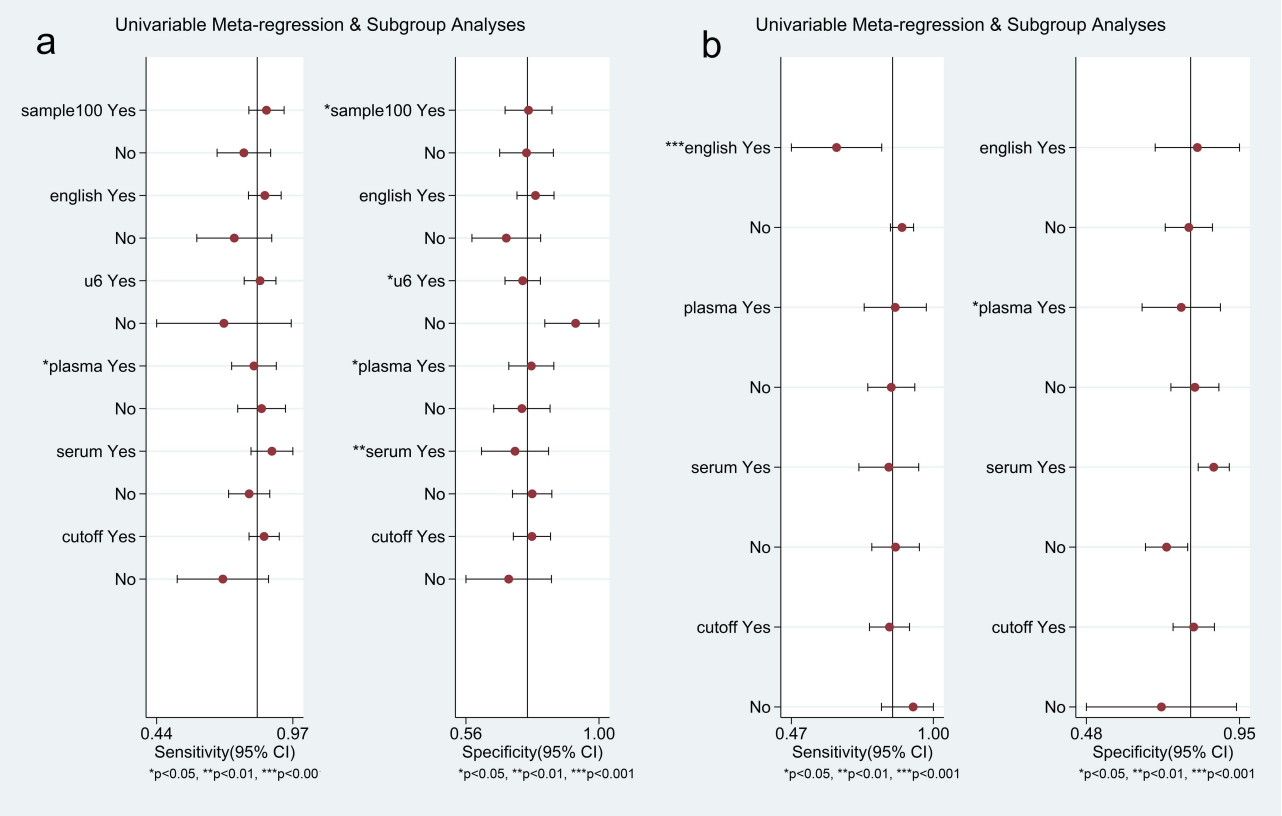

Figure 4 (**a**) The results of univariable meta-regression and subgroup analyses.(**a**) The blood miRNA was utilized to differentiate between COPD patients and the healthy control group in the meta-analysis results. (**b**) The blood miRNA was utilized to differentiate between AECOPD patients and the SCOPD patients in the meta-analysis results.

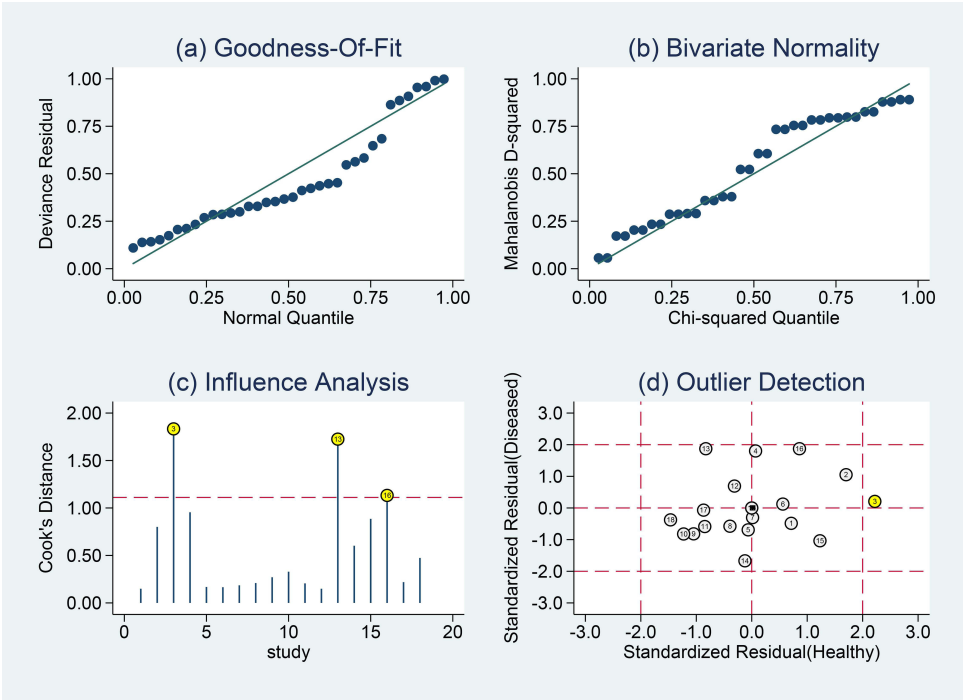

Figure 5 The sensitivity analysis was conducted using blood miRNA to distinguish between COPD patients and the healthy control group. (**a**) goodness-of-fit, (**b**) bivariate normality, (**c**) influence analysis, and (**d**) outlier detection.

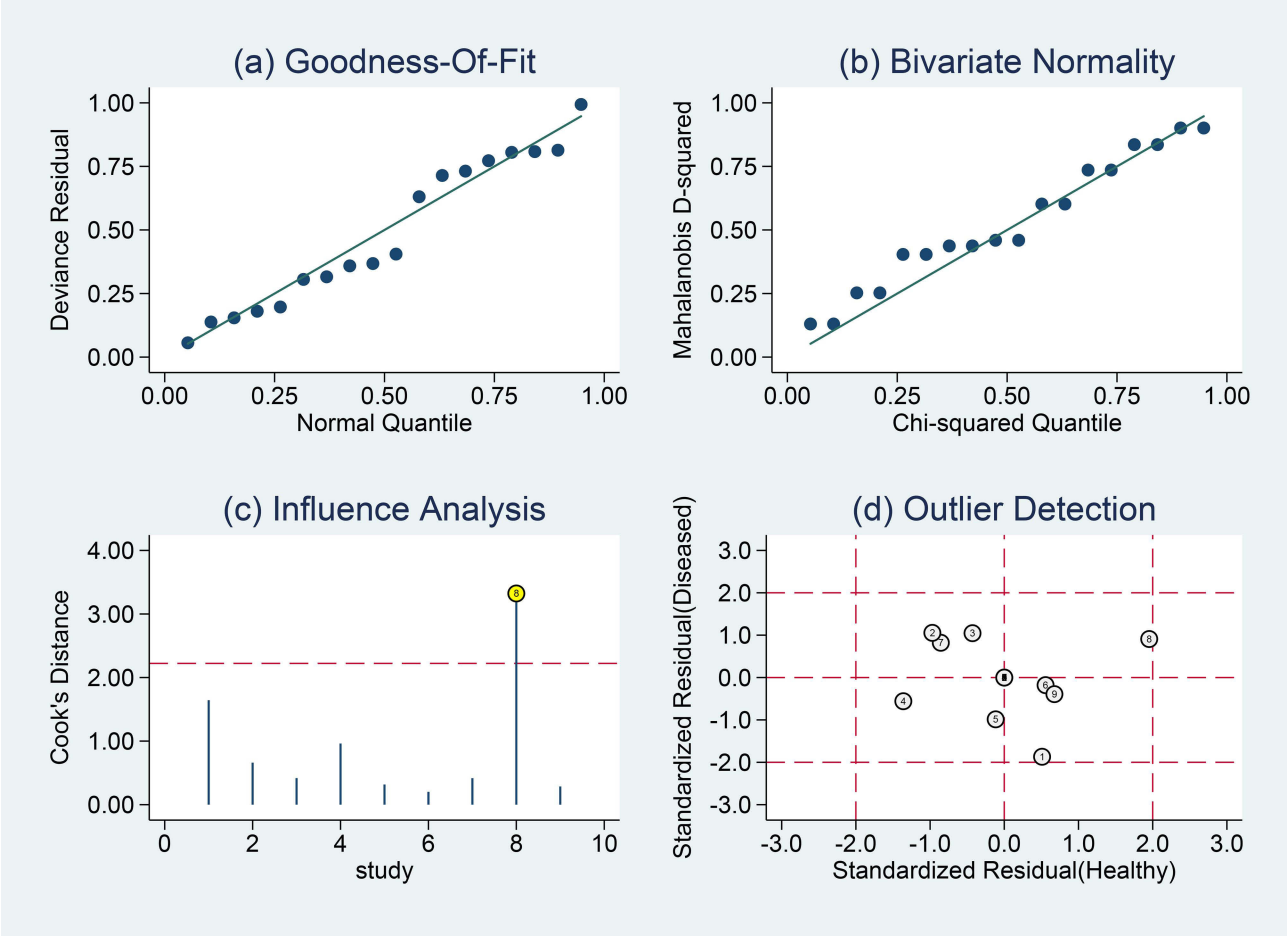

Figure 6 The sensitivity analysis was conducted using blood miRNA to distinguish between AECOPD patients and the SCOPD patients. (**a**) goodness-of-fit, (**b**) bivariate normality, (**c**) influence analysis, and (**d**) outlier detection.

and 1 outlier was detected through outlier detection (Figure 5c and d). After excluding these three studies, new results indicated that SSEN was 0.83 (95% CI 0.74–0.90), SSPE was 0.77 (95% CI 0.71–0.83), SPLR was 3.6 (95% CI 2.9–4.6), SNLR was 0.22 (95% CI 0.14–0.34), and DOR was 17 (95% CI 10–29). The AUC was 0.85 (95% CI 0.82–0.88). For the meta-analysis of blood miRNAs used in diagnosing AECOPD, goodness of fit and bivariate normal analyses (Figure 6a and b) showed that the bivariate model was robustly modeled. Influence analysis identified 1 outlier, and 1 outlier was found through outlier detection (Figure 6c and d). After excluding this study, new results indicated that SSEN is 0.79 (95% CI 0.72–0.84), SSPE is 0.74 (95% CI 0.68–0.79), SPLR is 3.0 (95% CI 2.4–3.9), SNLR is 0.29 (95% CI 0.21–0.39), and DOR is 11 (95% CI 6–18). The AUC was 0.83 (95% CI 0.79–0.86). Overall, the merged results after removing these outlier studies showed little change, indicating that our meta-analysis results were robust.

Discussion

As a prevalent respiratory condition, COPD is characterized by a gradual decline in lung function. Typically, COPD patients are typically susceptible to acute exacerbations (AECOPD), which contribute to a notable surge in incidence and mortality rates.[3] Consequently, early and prompt diagnosis holds paramount importance for individuals affected by COPD. In this comprehensive meta-analysis, we systematically searched numerous Chinese and English databases, rigorously adhering to predetermined inclusion and exclusion criteria to ensure the inclusion of high-quality literature. Ultimately, we identified 16 high-quality studies. The findings of the meta-analysis suggest that miRNA in the blood exhibits potential as a biomarker for distinguishing COPD patients from healthy individuals, as well as for discriminating between AECOPD and stable COPD (SCOPD) patients. However, it is crucial to acknowledge significant heterogeneity

in this meta-analysis, which arises from variations in language, sample types (serum or plasma), sample sizes, and miRNA normalizers.

MiRNA has emerged as a versatile biomarker with clinical applications across various respiratory diseases, including lung cancer,[33] asthma,[34] and pulmonary tuberculosis,[35] offering potential for disease diagnosis and staging. Recent research has shed light on a significant association between miRNA and COPD. Investigations emphasize the pivotal role of miRNA in COPD pathogenesis, regulating key signaling pathways such as MAPK, Wnt, NF-κB, and JAK-STAT, thereby contributing to lung development, maturation, and overall pulmonary function maintenance.[36–38] A critical aspect of COPD pathogenesis involves the apoptosis and proliferation of bronchial epithelial cells triggered by chronic inflammation. Several miRNAs, including miR-24-3p, miR-93-5p, miR-320a/b, and miR-1273-3p, have been identified as key players in airway inflammation, targeting pro-inflammatory genes and enriching pathways like NOD-like receptors and Toll-like receptor pathways.[39] Additionally, miR-233 has been shown to regulate HDAC2 expression and activity in lung cells, influencing pulmonary inflammation in COPD.[40] The study by Izzotti et al analyzed the down-regulation of 126 miRNAs in the lungs of rats exposed to a cigarette smoke environment and these miRNAs primarily regulate stress response, apoptosis, cell proliferation and angiogenesis, suggesting their potential relevance to the injury and repair processes in COPD.[41]

Immune dysregulation stands as another crucial pathogenic factor in COPD. Shi et al demonstrated in their study that miR-203 acts as an immune response inhibitor by targeting the TAK1 and PIK3CA genes. Their findings suggest that miR-203 may contribute to the onset and progression of COPD by suppressing the immune response in smokers.[42] Significant alterations in miRNA expression profiles have been reported in regulatory T cells from COPD patients. Among these, miR-199a-5p, specific to regulatory T cells, is implicated in the development of COPD by influencing the Th1-Th17 balance. Autophagy and apoptosis are additional key players in COPD pathogenesis.[43] miR-21 is implicated in cigarette smoke-induced autophagy and apoptosis in human bronchial epithelial cells.[44] Furthermore, miR-34a overexpression significantly increases apoptosis in human pulmonary microvascular endothelial cells. Notably, the protective effect of Notch1 overexpression mitigates the apoptosis induced by elevated miR-34a in human pulmonary microvascular endothelial cells.[45]

Blood marker detection has the advantages of convenience, speed, and strong repeatability. This meta-analysis found that blood miRNA holds potential for the diagnosis of COPD. However, the study also faces a significant heterogeneity issue. Differences in sample sizes result in significant heterogeneity, due to small-sample studies susceptible to result instability. While miRNA samples all come from blood, they can be further categorized into plasma and serum. Studies have shown significant differences in the quantity and types of miRNA between plasma and serum, leading to significant heterogeneity when combining different blood samples.[46] Moreover, the use of different miRNA internal references (whether U6) also causes variations in miRNA measurements.[47] In the discrimination diagnosis of blood miRNA for AECOPD and SCOPD patients, heterogeneity arises not only from the source of blood samples but also from the publication language. This may be influenced by publication bias, as Chinese studies might be more likely to be published in journals of their native language. This could result in differences in samples and methods among studies included in the meta-analysis. Besides, incorporating miRNA diagnostics into routine hospital labs presents challenges, notably the high cost and technical complexity of current polymerase chain reaction technology, which limits its widespread adoption. Transitioning these technologies from research settings to clinical practice requires addressing these barriers, possibly through developing cost-effective, simpler alternatives like paper-based biosensors.[48,49]

In our study, we highlighted the potential of blood miRNAs as diagnostic biomarkers for COPD. However, the practical application of miRNA measurement is currently limited by the need for sophisticated laboratory equipment and specialized technical expertise, making widespread implementation challenging, particularly in resource-constrained settings. Comparatively, spirometry, the standard diagnostic tool for COPD, is recognized for its simplicity and low cost but is not universally available, especially in low-income regions. This disparity underscores the significance of developing complementary diagnostic approaches, like miRNA testing, which could serve as an invaluable tool in areas lacking spirometry facilities. To enhance the global accessibility and feasibility of miRNA-based diagnostics, innovative solutions are necessary. Future research could focus on simplifying detection methods, such as developing cost-effective,

paper-based assays suitable for use in low-resource settings. Integrating miRNA testing with simplified pulmonary function tools could offer a pragmatic and affordable solution, facilitating broader COPD diagnosis coverage.

We acknowledge several limitations in our meta-analysis. Firstly, our study exclusively incorporated published literature in both Chinese and English, omitting some studies in other languages and grey literature, potentially introducing bias into the results. Secondly, despite the inclusion of 16 articles, the majority originated from China and Japan, representing exclusively Asian populations. Consequently, the lack of data from other ethnic groups, such as Caucasians and black individuals, may limit the global generalizability of our study's conclusions. Lastly, our meta-analysis exhibited heterogeneity, even though we utilized univariate metaregression analysis and subgroup analysis to identify potential sources of heterogeneity.

Conclusion

Blood miRNA has demonstrated promising diagnostic potential as a non-invasive biomarker for COPD patients, especially within the Chinese population. However, to substantiate this conclusion, additional large-scale and well-designed prospective studies are warranted.

Data Sharing Statement

The data analyzed in this meta-analysis were exclusively derived from previously published literature.

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Disclosure

The authors declare that they have no competing interests in this work.

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