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Circulating Microrna-19 as a Non-Invasive Biomarker for Detecting Lung Cancer: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies

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ABSTRACT

Invasive procedures remain the gold standard for lung cancer diagnosis, while new cases in 2018 reached 30,023 patients and tend to occur at a younger age, necessitating non-invasive markers for early detection of lung cancer. Currently, numerous studies have been conducted on microRNA (miRNA) as a lung cancer biomarker, including miRNA-19; however, research findings on miRNA-19 in the diagnosis of this disease remain controversial, prompting this study to assess the ability of miRNA-19 to detect lung cancer through a meta-analysis. Literature searches were conducted in three databases (PubMed, Science Direct, and Cochrane) up to March 22, 2023, using the Patient, Intervention, Comparison, Outcome (PICO) principle, with inclusion criteria for prospective, retrospective, case-control, or cross-sectional studies providing data for analyzing the diagnostic capability of miRNA-19. The methods used adhere to the 2020 PRISMA guidelines. Analysis was performed using STATA, MetaDisc, and Review Manager software. Four articles met the inclusion criteria for this meta-analysis. The combined analysis results regarding the sensitivity of miRNA-19 in lung cancer diagnosis reached 0.81 (95% CI [confidence interval]: 0.76–0.85), specificity 0.69 (95% CI: 0.61–0.76), diagnostic odds ratio (DOR) 12.62 (95% CI: 4.73–33.65), and area under the curve (AUC) 0.85. Analysis of the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) yielded results... Analysis of the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) yielded results 2.51 (95% CI: 1.59–3.95) and 0.29 (95% CI: 0.18–0.48). Based on the above data, miRNA-19 has potential in the non-invasive diagnosis of lung cancer.

KEYWORDS *miRNA-19, lung cancer, diagnosis*

INTRODUCTION

Lung cancer, the leading cause of cancer-related deaths worldwide, is a health issue that impacts morbidity, mortality, and the economy, potentially disrupting healthcare systems. In 2018, the World Health Organization (WHO) reported 30,023 new cases of lung cancer in younger age groups and 26,095 lung cancer-related deaths in Indonesia. Patients often present at an advanced stage because diagnosing early-stage lung cancer is extremely challenging due to non-specific clinical presentations. Therefore, there is an urgent need to screen high-risk patients. If detected early, the five-year survival rate for early-stage lung cancer is significantly higher than that for advanced-stage lung cancer (Li et al., 2022). Currently, low-dose computed tomography (LDCT) is routinely used for lung cancer screening. However, recent studies indicate that the false-positive rate of LDCT reaches 81% (Nooreldeen & Bach, 2021). Biopsy is the gold standard for diagnosis, but this procedure is prone to complications such as pneumothorax and hemothorax (Gartmant et al., 2018). Additionally, biopsy is an invasive procedure, and sometimes the specimen location is difficult to access, with a high risk of obtaining an inappropriate specimen (no malignant cells). Therefore, a non-invasive marker is needed for early detection of lung cancer with adequate sensitivity and specificity.

Micro-ribonucleic acid (microRNA/miRNA) is a short non-coding RNA molecule consisting of 20–22 nucleotides that can induce degradation or inhibit translation of target genes by binding to the 3'-untranslated region (3'-UTR) of messenger RNA (mRNA) (Xia et al., 2017). MicroRNA is expressed differently in normal and cancerous tissues and contributes to the initiation, progression, metastasis, and angiogenesis of cancer (Peng et al., 2018). MicroRNA-19 is known as an important miRNA in the miR-17-92 oncomiR cluster (Rupaimoole & Slack, 2017). In lung cancer, miRNA-19 plays a role in cancer cell invasion and migration (Feng et al., 2014).

Numerous studies have been conducted to assess the ability of miRNA-19 to detect lung cancer. MicroRNA-19 is believed to have the capacity to detect cancer. However, the results of some studies remain inconsistent (Li et al., 2015). Zaporozhchenko et al. (2016) found that the sensitivity of miRNA-19 for diagnosing lung cancer was 0.68, while Qiu et al. (2018) found that the sensitivity of miRNA-19 could reach 0.98. Therefore, to accurately evaluate the diagnostic value of miRNA-19, we conducted this meta-analysis study.

This study addresses the controversial and inconsistent findings in existing research regarding the diagnostic accuracy of *microRNA-19* (miRNA-19) as a biomarker for lung cancer. While previous studies have explored miRNA-19's role, results vary widely—for instance, reported sensitivities range from 0.68 to 0.98. By conducting a systematic review and meta-analysis of diagnostic test accuracy studies, this research provides a comprehensive evaluation of miRNA-19's performance, synthesizing fragmented evidence into a unified conclusion. Additionally, the study adheres to the rigorous PRISMA 2020 guidelines and employs advanced statistical tools (STATA, MetaDisc, and Review Manager) to ensure robust and reproducible results.

The main objective of this study was to assess the diagnostic accuracy of miRNA-19 as a non-invasive biomarker for lung cancer. Specifically, this study aims to: (1) determine the sensitivity, specificity, and area under the curve (AUC) of combined miRNA-19 in detecting lung cancer; (2) evaluate the diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) to measure the clinical utility of miRNA-19; and (3) identify sources of heterogeneity between studies to explain differences in the existing literature.

The findings of this study have great potential for clinical and public health applications. First, in terms of clinical utility, validated miRNA-19 can be an effective and non-invasive early detection tool for lung cancer, complementing or reducing reliance on invasive procedures. Second, early diagnosis facilitated by miRNA-19 can improve survival rates by allowing for more timely interventions. Third, from the aspect of research development, this meta-analysis is the basis for further studies of miRNA-19 in various populations and settings, especially in resource-constrained areas such as Indonesia, where high diagnostic costs are still a barrier. By highlighting these aspects, this study not only contributes to the development of precision oncology but also confirms the transformative potential of miRNA-based diagnostics in lung cancer management.

METHOD

A meta-analysis study was conducted to evaluate the role of miRNA-19 in detecting lung cancer. The literature search used a combination of keywords consistent with the *"Patient, Intervention, Comparison, Outcome"* (PICO) principle; the keywords included "(microRNA-

19 OR miRNA-19 OR miR-19) AND (lung cancer OR lung carcinoma OR lung tumor) AND (diagnosis OR sensitivity OR specificity)." Two authors (JAFK and HAA) independently searched for literature data from the PubMed, Science Direct, and Cochrane databases up to March 22, 2023. All articles from the three databases were collected to analyze the diagnostic capability of miRNA-19. The guidelines used in this analysis were the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020.

2.1. Inclusion and exclusion criteria

Inclusion criteria were established to ensure that only relevant publications were included in our analysis. We used the following criteria: (1) confirmed lung cancer patients as the study group and healthy individuals as the control group; (2) studies with retrospective, prospective, case-control, or cross-sectional designs, as well as studies obtained through manual searches; (3) providing data for calculating the diagnostic value of miRNA-19; (4) in English; and (5) lung cancer diagnosis based on miRNA-19 supported by pathological evidence from biopsy or surgical resection.

The exclusion criteria were as follows: (1) non-English literature; (2) irrelevant titles and/or abstracts, reviews, conference papers, and animal experiments; (3) combined analysis of miRNA-19 with other miRNAs in lung cancer diagnosis; and (4) data unavailable for calculating the diagnostic value of miRNA-19.

Data extraction and quality assessment

From each study that met the inclusion criteria, the following data were extracted: (1) first author's name; (2) year of publication; (3) country; (4) specimen type; (5) number of samples; (6) type of lung cancer; and (7) information for assessing diagnostic capability (sensitivity, specificity, false negative [FN], true negative [TN], true positive [TP], and false positive [FP]). The collected data were organized using Microsoft Excel 365 to facilitate analysis.

The quality of the publications included in this meta-analysis was evaluated using the *"Quality Assessment of Diagnostic Accuracy Studies-2"* (QUADAS-2). After a thorough review, four domains (patient selection, index test, reference standard, and flow and timing) were analyzed according to the criteria "Yes," "No," and "Unclear." Cross-checking was performed and reviewed independently by two researchers (JAFK and HAA) and discussed with a third researcher (RMAN) in case of disagreement until consensus was reached.

Statistical analysis

The statistical analysis process used STATA software version 17.0, MetaDisc, and Review Manager version 5.4.1. A variable classification model was used to calculate pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and 95% confidence interval (95% CI), as well as to generate a summary receiver operating characteristic (SROC) curve (Sun et al., 2020). The area under the curve (AUC) of the SROC curve was assessed on a scale of 0.5 to 1.0; if the AUC value was close to 0.5, the diagnostic ability was considered poor; if the AUC value was close to 1.0, the diagnostic ability was considered good. The p-heterogeneity test and inconsistency index (I^2) were used to assess the level of heterogeneity. Two authors (JAFK and HAA) performed the statistical analysis independently to avoid inaccuracies.

RESULT AND DISCUSSION

Literature search and characteristics

A total of 146 articles were obtained based on the combination of keywords used. After eliminating duplicate studies, 108 articles passed the initial screening process, resulting in 35 articles. Four articles were selected for this meta-analysis (Zaporozhchenko et al., 2016; Qiu et al., 2018; Fan et al., 2016; Yang et al., 2020). The literature search process is shown in the PRISMA 2020 flow diagram (Figure 1). The characteristics of the studies we analyzed are presented in Table 1 and Table 2.

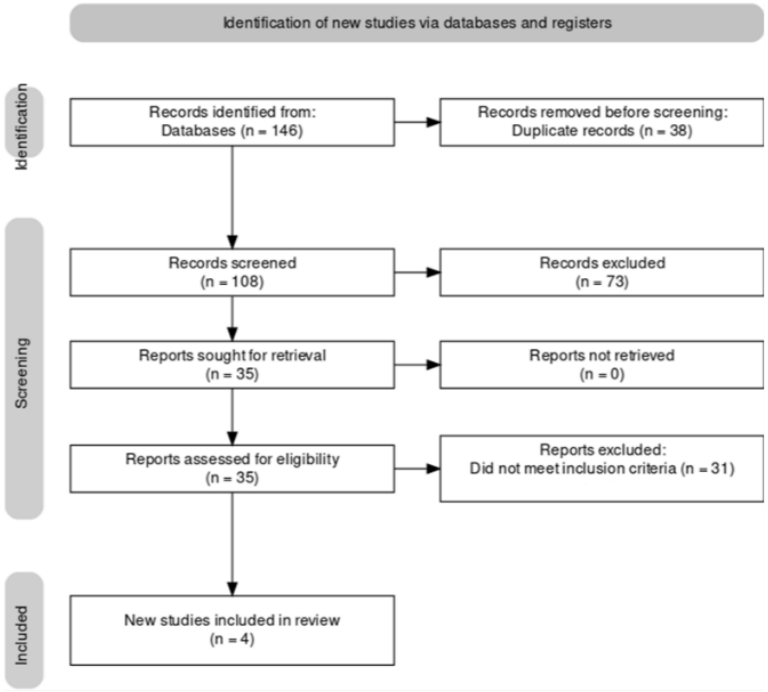


Table 1. Article Characteristics

First author, year	Country	Specimens	Number of samples (cases/controls)	Landfill	FNb	Fpc	TNd
Fan, 2016 [17]	Chinese	Serum	94/58	78	16	19	39
Zaporozhchenko, 2016 [12]	Russia	Plasma	75/50	51	24	4	46
StuRat (talk) 13:00, 13 January 2018 (UTC)	Chinese	Serum	58/42	57	1	20	22
Yang, 2020 [18]	Chinese	Serum	74/23	58	16	11	12

[a] TP = *true positive*; [b] FN = *false negative*; [c] FP = *false positive*; [d] TN = *true negative*

Table 2. Article Characteristics

First author, year	Sensitivity	Specificity	Types of lung cancer	Control group
Fan, 2016 [17]	83.1%	66.7%	NSCLCa	Healthy individuals
Zaporozhchenko, 2016 [12]	68.9%	93%	LCb	Healthy individuals
StuRat (talk) 13:00, 13 January 2018 (UTC)	98.3%	54.29%	LCb	Healthy individuals
Yang, 2020 [18]	78.85%	55.56%	NSCLCa	Healthy individuals

[a] NSCLC = *non-small cell lung cancer*; [b] LC = *lung cancer*

Data analysis

A total of 474 patients were included in this meta-analysis (301 patients in the lung cancer group and 173 patients in the control group). The results of the analysis from four studies showed a pooled sensitivity of miRNA-19 for lung cancer diagnosis of 0.81 (95% CI: 0.76–0.85), specificity of 0.69 (95% CI: 0.61–0.76), PLR of 2.51 (95% CI: 1.59–3.95), NLR of 0.29 (95% CI: 0.18–0.48), DOR of 12.62 (95% CI: 4.73–33.65), and AUC of 0.85. Results are presented in Figures 2–4. Pre-test probability in Fagan's Nomogram was selected according to lung cancer prevalence (Safari et al., 2016; Chen et al., 2022). Evaluation of study quality using the QUADAS-2 ranking scale yielded high overall article quality (Figure 5).

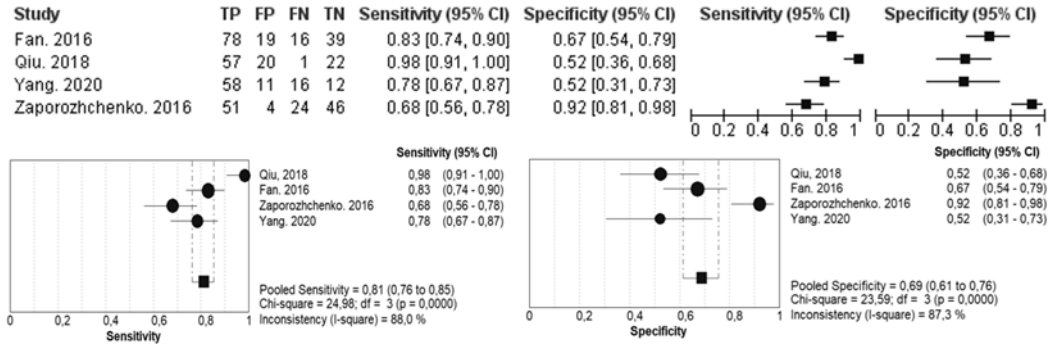
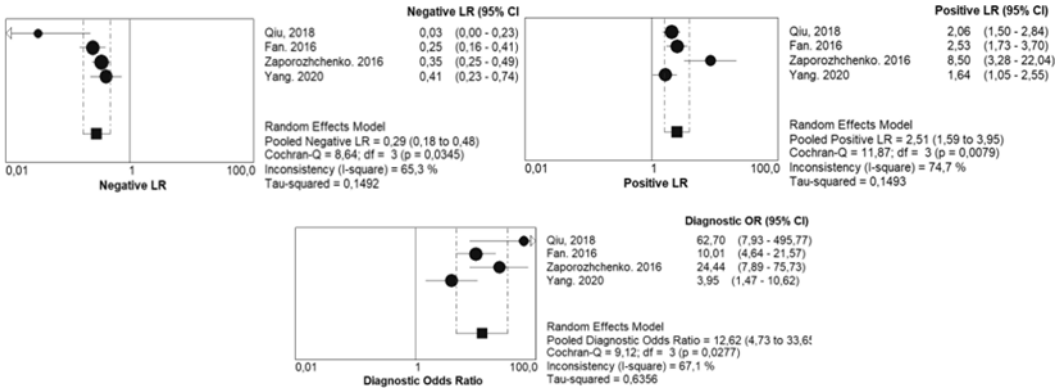
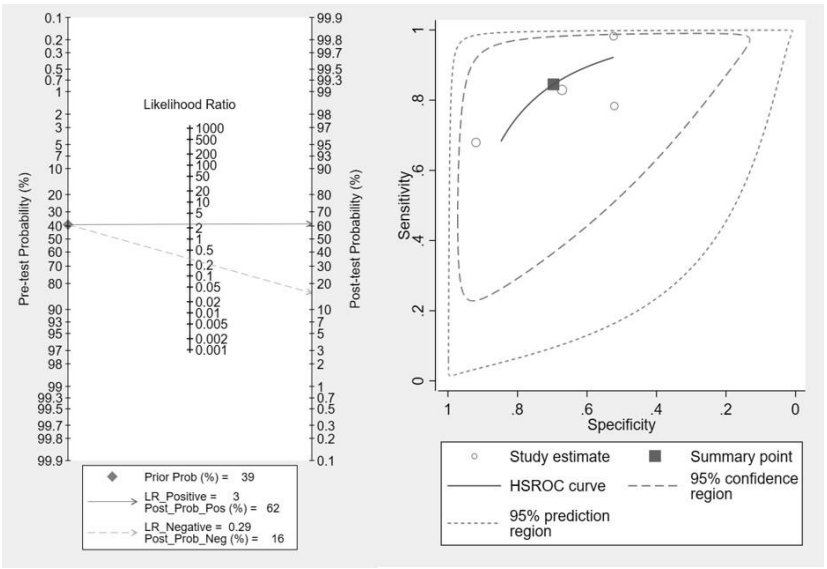
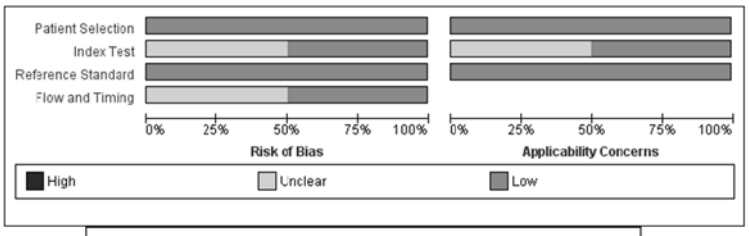


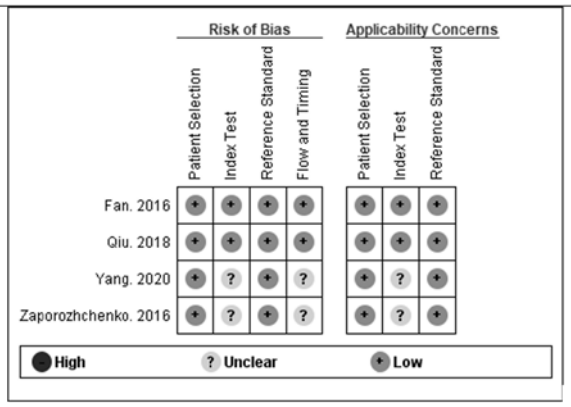
Figure 3. Forest Plot of Negative Likelihood Ratio, Positive Likelihood Ratio, and Diagnostic



Odds Ratio *LR = *likelihood ratio*; 95% CI = 95% *confidence interval*







miRNA-19 and lung cancer

Early diagnosis is key to improving the success of cancer therapy. Currently, the gold standard for diagnosing lung cancer is through surgical procedures or invasive examinations such as bronchoscopy, transthoracic needle aspiration, or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (Chen et al., 2012). The current method for screening high-risk patients is through X-rays and CT scans. However, these examinations provide less accurate results if the patient has very small nodules, and repeated radiation exposure can be harmful to the patient (Fan et al., 2016). Therefore, a non-invasive marker is needed to detect malignancy in the lungs to reduce morbidity and mortality from lung cancer.

MicroRNA is a class of non-coding RNA molecules that can influence mRNA stability and translation processes by binding to complementary regions in the 3'UTR of target mRNA, thereby participating in gene expression regulation (Mitra et al., 2020). In blood and plasma, miRNA is stable, and most undergo deregulation in cancer cells. miRNA analysis has developed rapidly in recent years due to the availability of polymerase chain reaction (PCR) technology. Many miRNAs exhibit different expression patterns in lung cancer patients,

making them potential targets for diagnosis, prognosis, and therapy (Xu et al., 2014; Gao et al., 2012).

Overall, our current analysis suggests that miRNA-19 may be a biomarker capable of detecting lung cancer. These promising results may be related to miRNA-19's role as an oncomiR or oncogenic miRNA (Li et al., 2020; Feng et al., 2014). Several studies have reported increased miRNA-19 expression in lung cancer patients (Peng et al., 2018; Li et al., 2015; Zhu et al., 2021). Li et al. (2015). Li et al. (2015) reported that upregulation of miRNA-19 triggers epithelial-mesenchymal transition (EMT) in lung cancer cells, which can support cancer cell invasion and migration. This is supported by research conducted by Guinot et al. (2016), where miRNA-19 expression can activate Wnt signaling by targeting p38α in non-small cell lung cancer (NSCLC) and increase the malignant potential of NSCLC.

Through the analysis of these four studies, the sensitivity of miRNA-19 in lung cancer diagnosis reached 0.81 (95% CI: 0.76 – 0.85), specificity 0.69 (95% CI: 0.61 – 0.76), and AUC 0.81. These three representative parameters validate the diagnostic accuracy of miRNA-19 in patients with lung cancer. In addition, the DOR value of 12.62 (95% CI: 4.73 – 33.65) and post-test probability of PLR 62% and NLR 16% support the ability of miRNA-19 as a lung cancer marker.

Our analysis has several limitations, such as the implementation of miRNA-19 testing in Indonesia. MiRNA-19 detection can be performed using reverse transcription quantitative PCR (RT-qPCR) (Androvic et al., 2017). However, the cost of using this diagnostic tool in Indonesia is quite high, so further exploration of this test for early lung cancer detection is needed to reduce morbidity and mortality (Rahmasari et al., 2022). Furthermore, this meta-analysis used a small sample size and may not be representative of the population. This is due to the limited number of studies evaluating the specific ability of miRNA-19 in detecting lung cancer. Furthermore, we did not perform further sensitivity analysis regarding the heterogeneity of the included studies. Therefore, further research with a larger sample size is needed to evaluate miRNA-19 as a non-invasive marker in lung cancer detection.

CONCLUSION

Our meta-analysis included four studies that assessed the diagnostic ability of miRNA-19 in detecting lung cancer. In general, miRNA-19 can be used as a non-invasive marker for lung cancer, supported by satisfactory diagnostic ability analysis results. However, further research with an adequate sample size is needed. Other recommendations include standardization of detection methods, cost-effectiveness analysis (especially in low-income countries such as Indonesia), as well as exploration of combining miRNA-19 with other biomarkers to improve diagnostic accuracy. Longitudinal studies are also needed to assess its potential in monitoring therapeutic responses. The clinical implementation of miRNA-19 as a diagnostic tool requires further refinement to overcome the limitations of current studies.

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