INPLASY PROTOCOL

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None declared.

Circulating MicroRNAs as Potential Diagnostic Biomarkers for Cervical Intraepithelial Neoplasia and early Cervical Cancer : A Systematic Review and Meta-Analysis

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Review question / Objective: **Cervical cancer is the predominant form of malignancy affecting the female reproductive system, with cervical intraepithelial neoplasia (CIN) serving as its precursor lesion, capable of advancing to invasive cervical cancer (CC). Despite limited investigations examining circulating microRNAs (miRNAs) as potential diagnostic biomarkers for CIN and early-CC, the results have been conflicting. In light of these discrepancies, this meta-analysis was undertaken to assess the diagnostic accuracy of miRNAs for CIN and early-CC, and identify possible sources of heterogeneity across studies.**
Eligibility criteria: **The inclusion criteria were as follows: (1) studies must be relevant to the diagnostic performance of circulating miRNAs for CIN or CC diagnosis; (2) the case group must consist of patients who were diagnosed using clinically recognized diagnostic criteria; and (3) the frequencies of false positive (FP), true positive (TP), false negative (FN), and true negative (TN) could be extracted directly or indirectly from the studies. By contrast, studies meeting any of the following exclusion criteria were excluded: (1) cell, animal, or microbiological trials; (2) non-case-control studies; and (3) reviews, meta-analyses, or conference abstracts.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 April 2023 and was last updated on 17 April 2023 (registration number INPLASY202340053).

INTRODUCTION

Review question / Objective: **Cervical cancer is the predominant form of malignancy affecting the female reproductive system, with cervical intraepithelial neoplasia (CIN) serving as its precursor lesion, capable of advancing to invasive cervical cancer (CC). Despite limited investigations examining circulating**

microRNAs (miRNAs) as potential diagnostic biomarkers for CIN and early-CC, the results have been conflicting. In light of these discrepancies, this meta-analysis was undertaken to assess the diagnostic accuracy of miRNAs for CIN and early-CC, and identify possible sources of heterogeneity across studies.

Condition being studied: Cervical cancer is the predominant form of malignancy affecting the female reproductive system, with cervical intraepithelial neoplasia (CIN) serving as its precursor lesion, capable of advancing to invasive cervical cancer (CC). The development of cervical cancer from cervical intraepithelial neoplasia (CIN) may take several years or even decades. Early diagnosis and treatment of CIN or early-stage cervical cancer confer more favorable clinical outcomes than advanced-stage cervical cancer. However, due to its asymptomatic and nonspecific nature in the early stages, a considerable proportion of cervical cancer (CC) cases are diagnosed at later stages . Consequently, early identification of cervical intraepithelial neoplasia (CIN) or early-stage CC is of utmost importance. Several screening methods have been developed to detect CIN or early CC, including HPV DNA testing, Papanicolaou (Pap) smear, liquid-based cytology (LBC) , colposcopy, etc. Nevertheless, these methods have certain limitations, such as false-positive rate, false-negative rate, overdiagnosis, missed diagnosis, invasiveness, and variation among pathologists, etc.Hence, the development of simple, noninvasive, and practical biomarkers for detecting CIN and early-stage CC is an urgent need. MicroRNAs (miRNAs) are endogenous non-coding regulatory RNAs of approximately 22 nucleotides in length. These molecules play a critical role in regulating physiological and pathological processes by inhibiting or degrading the miRNAs of target genes. While miRNAs are typically localized within the cytoplasm, they can also be released into the extracellular space upon maturation. Furthermore, some miRNAs can evade degradation by RNA enzymes due to their interaction with RNA-binding proteins or exosomes, allowing for their stable presence in various bodily fluids, such as serum, plasma, and other fluids. Recent studies have demonstrated that circulating miRNAs can serve as useful biomarkers for various types of cancers, including breast cancer (BC) , pancreatic cancer, non-small cell lung cancer, cervical cancer, and cervical intraepithelial neoplasia (CIN),etc. Importantly, changes in miRNA expression levels have been detected in these cancers even before standard diagnostic tools could identify the presence of tumors . Given their stability, widespread distribution, high specificity, sensitivity, ease of detection and analysis, and relatively low cost, miRNAs have the potential to serve as promising novel biomarkers for the diagnosis of CIN and early-CC. Despite limited investigations examining circulating microRNAs (miRNAs) as potential diagnostic biomarkers for CIN and early-CC, the results have been conflicting. In light of these discrepancies, this meta-analysis was undertaken to assess the diagnostic accuracy of miRNAs for CIN and early-CC, and identify possible sources of heterogeneity across studies.

METHODS

Search strategy: ((((("Uterine Cervical Dysplasia"[Mesh]) OR ((((((((((((((((((((Cervical Dysplasia, Uterine[Title/Abstract]) OR (Dysplasia, Uterine Cervical[Title/Abstract])) OR (Dysplasia of Cervix Uteri[Title/Abstract])) OR (Cervix Uteri Dysplasia[Title/Abstract])) OR (Cervix Uteri Dysplasias[Title/Abstract])) OR (Cervical Intraepithelial Neoplasia[Title/Abstract])) OR (Cervical Intraepithelial Neoplasms[Title/Abstract])) OR (Cervical Intraepithelial Neoplasm[Title/Abstract])) OR (Intraepithelial Neoplasm, Cervical[Title/Abstract])) OR (Intraepithelial Neoplasms, Cervical[Title/Abstract])) OR (Neoplasm, Cervical Intraepithelial[Title/Abstract])) OR (Neoplasms, Cervical Intraepithelial[Title/Abstract])) OR (Intraepithelial Neoplasia, Cervical[Title/Abstract])) OR (Neoplasia, Cervical Intraepithelial[Title/Abstract])) OR (Cervical Dysplasia[Title/Abstract])) OR (Cervical Dysplasias[Title/Abstract])) OR (Dysplasia,

Cervical[Title/Abstract])) OR (Cervix Dysplasia[Title/Abstract])) OR (Dysplasia, Cervix[Title/Abstract])) OR (Cervical Intraepithelial Neoplasia, Grade III[Title/Abstract]))) OR (("Uterine Cervical Neoplasms"[Mesh]) OR ((((((((((((((((((((((((Cervical Neoplasm, Uterine[Title/Abstract]) OR (Cervical Neoplasms, Uterine[Title/Abstract])) OR (Neoplasm, Uterine Cervical[Title/Abstract])) OR (Neoplasms, Uterine Cervical[Title/Abstract])) OR (Uterine Cervical Neoplasm[Title/Abstract])) OR (Neoplasms, Cervical[Title/Abstract])) OR (Cervical Neoplasms[Title/Abstract])) OR (Cervical Neoplasm[Title/Abstract])) OR (Neoplasm, Cervical[Title/Abstract])) OR (Neoplasms, Cervix[Title/Abstract])) OR (Cervix Neoplasms[Title/Abstract])) OR (Cervix Neoplasm[Title/Abstract])) OR (Neoplasm, Cervix[Title/Abstract])) OR (Cancer of the Uterine Cervix[Title/Abstract])) OR (Cancer of the Cervix[Title/Abstract])) OR (Cervical Cancer[Title/Abstract])) OR (Uterine Cervical Cancer[Title/Abstract])) OR (Cancer, Uterine Cervical[Title/Abstract])) OR (Cancers, Uterine Cervical[Title/Abstract])) OR (Cervical Cancer, Uterine[Title/Abstract])) OR (Cervical Cancers, Uterine[Title/Abstract])) OR (Uterine Cervical Cancers[Title/Abstract])) OR (Cancer of Cervix[Title/Abstract])) OR (Cervix Cancer[Title/Abstract])) OR (Cancer, Cervix[Title/Abstract])) OR (Cancers, Cervix[Title/Abstract]))))) AND ((("MicroRNAs"[Mesh]) OR ((((((((((((((((((MicroRNA[Title/Abstract]) OR (miRNAs[Title/Abstract])) OR (Micro RNA[Title/Abstract])) OR (RNA, Micro[Title/Abstract])) OR (miRNA[Title/Abstract])) OR (Primary MicroRNA[Title/Abstract])) OR (MicroRNA, Primary[Title/Abstract])) OR (Primary miRNA[Title/Abstract])) OR (miRNA, Primary[Title/Abstract])) OR (pri-miRNA[Title/Abstract])) OR (pri miRNA[Title/Abstract])) OR (RNA, Small Temporal[Title/Abstract])) OR (Temporal RNA, Small[Title/Abstract])) OR (stRNA[Title/Abstract])) OR (Small Temporal RNA[Title/Abstract])) OR (pre-miRNA[Title/Abstract])) OR (pre miRNA[Title/Abstract]))))) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR (predictive[Title/Abstract] AND value*[Title/Abstract]) OR predictive value of tests[MeSH Term] OR accuracy*[Title/Abstract]).

Participant or population: Cervical Intraepithelial Neoplasia and early Cervical Cancer.

Intervention: microRNAs expression.

Comparator: Patients that are not related to cervical intraepithelial neoplasia and cervical cancer or healthy controls. Patients that was not related to cervical intraepithelial neoplasia and cervical cancer or healthy controls.

Study designs to be included: RCT or cohort study.

Eligibility criteria: The inclusion criteria were as follows: (1) studies must be relevant to the diagnostic performance of circulating miRNAs for CIN or CC diagnosis; (2) the case group must consist of patients who were diagnosed using clinically recognized diagnostic criteria; and (3) the frequencies of false positive (FP), true positive (TP), false negative (FN), and true negative (TN) could be extracted directly or indirectly from the studies. By contrast, studies meeting any of the following exclusion criteria were excluded: (1) cell, animal, or microbiological trials; (2) non-case-control studies; and (3) reviews, meta-analyses, or conference abstracts.

Information sources: We search articles in PubMed, Cochrane Library, Embase, and Web of Science.

Main outcome(s): The pooled results for sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic (ROC) curve.

Quality assessment / Risk of bias analysis: The risk of bias and clinical applicability of all included studies were assessed independently by two reviewers using the

Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.

Strategy of data synthesis: We extracted the sample size, sensitivity, and specificity from every study to calculate the value of TP, FP, FN, and TN. Statistical analysis was conducted using Stata 14.0 software. The analysis included pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic ratio (DOR), and corresponding 95% confidence intervals (CI). Summary receiver operating characteristic (SROC) curves were also plotted to calculate the area under the curve (AUC), which was used to test the pooled diagnostic value of miRNAs. Besides, we explored the threshold effect based on Spearman's correlation coefficient and P value through Meta-DiSc 1.4 software . And the heterogeneity between studies was assessed using Cochran-Q test and I2 statistic for quantitative analysis. A P-value less than 0.05 for the Cochran-Q test and an I2 value greater than 50% indicated significant heterogeneity among studies, and thus we selected the random-effect model for the analysis. Subsequently, the main sources of heterogeneity were investigated via subgroup analyses and regression analysis. A sensitivity analysis was conducted to ascertain the reliability and robustness of the meta-analysis outcomes. Deeks' funnel plots were employed to examine any potential publication bias. Furthermore, to further evaluate the diagnostic effectiveness of miRNAs, a Fagan's nomogram was developed. The quality of the literature was assessed using Review Manager 5.4. A statistical significance level of P-value < 0.05 was employed to validate the results.

Subgroup analysis: In order to investigate the possibility of variations within the dataset, we conducted a subgroup analysis. Our grouping criteria included miRNA profiling(single vs multiple), type of comparison(CC/HC vs CIN/HC) , sample size(<100 vs ≥100) , miRNA expression (up-regulate vs down-regulate) , ethnicity (Asian vs Non-Asian) , and reference source(U6 vs Non-U6).

Sensitivity analysis: A sensitivity analysis was conducted to ascertain the reliability and robustness of the meta-analysis outcomes. We identified the sources of heterogeneity by excluding the outlier groups one by one.

Language restriction: All of the publications that were incorporated in the analysis were disseminated in the English language.

Country(ies) involved: China.

Keywords: miRNA, Cervical Cancer, Cervical Intraepithelial Neoplasia, biomarkers, meta-analysis.

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