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Kong, LS¹; Li, Y²; Yang, L³; Fan, JM⁴; Zhai, XS⁵; Zhao, XJ⁶; Wen, SX⁷.**ADMINISTRATIVE INFORMATION****Support** - Shanxi Children's Hospital & Shanxi Maternal and Child Health Hospital.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202360048**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 June 2023 and was last updated on 16 June 2023.**INTRODUCTION**

Review question / Objective The purpose of this systematic review was to systematically review the clinical studies regarding circulating microRNAs as diagnostic biomarkers for thyroid carcinoma and assess the overall diagnostic accuracy of miRNAs.

Condition being studied Thyroid carcinoma is a malignant tumor that originates from the epithelium of thyroid follicles or adjacent epithelial cells. The annual incidence rate of thyroid cancer with a diameter of <2.0 cm increased more than four times from 1983 to 2011 in the United States. The most common of the pathological type is papillary thyroid carcinoma(PTC), accounting for approximately 85% to 90% of all thyroid carcinomas. Considering that the vast majority of TC are occult and asymptomatic tumors, early

detection of TC is crucial to the prognosis and prevention of the disease. The current approaches for the diagnosis of thyroid carcinoma include ultrasound examination and fine-needle aspiration cytology(FNAC). The gold standard is postoperative histopathological examination. However, accurate diagnosis is heavily dependent on the technical performance and experience of the operators, particularly in the category of follicular neoplasms (FNs). Indeed, there is a general need for accurate TC biomarkers to better guide diagnostic and therapeutic decisions. More specifically, robust minimally invasive diagnostic biomarkers for TC would allow for the improvement in planning of TC screening and its early detection. MicroRNAs (miRNAs) are a class of non-coding RNA encoded by endogenous genes with a length of about 22 nucleotides. MiRNAs have been shown to perform a key role in essential cellular processes including development, cell

differentiation, inflammation, proliferation, apoptosis and tumorigenesis. MiRNAs are stable, noninvasive, and resistant to degradation by ribonucleases, making them valuable as a novel biomarker for the diagnosis of thyroid carcinoma. However, inconsistent results have been found about the diagnostic accuracy of miRNAs for TC.

METHODS

Participant or population Thyroid Carcinoma.

Intervention miRNAs expression.

Comparator Patients that are not related to thyroid carcinoma or healthy controls. Patients that was not related to thyroid carcinoma or healthy controls.

Study designs to be included No restrictions.

Eligibility criteria For subject recruitment, we set rigorous inclusion criteria to ensure the validity and reliability of our study : (1) all patients in the case group were diagnosed following clinically recognized diagnostic criteria; (2) the intervention was characterized by the diagnosis of TMN performed using miRNA examination; (3) false positive (FP), true positive (TP), false negative (FN), and true negative (TN) could be derived directly or calculated from the literature. Several exclusion criteria were implemented. Studies involving non-human trials, non-case-control designs, reviews, letters, or conference abstracts were eliminated from our analysis. Additionally, studies with insufficient data were also excluded to ensure that only high-quality research was included in our analysis.

Information sources We conducted a systematic search of PubMed, Embase, Web of Science, and Cochrane Library databases up until December 22, 2022.

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

Quality assessment / Risk of bias analysis The quality of studies was evaluated by two reviewers according to the quality assessment of diagnostic accuracy studies (QUADAS-2) tool using RevMan 5.3 software.

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 through RevMan 5.3 software. The statistical analysis of meta-analysis was conducted using Stata 14.0 software, providing pooled estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and summary receiver operating characteristic (sROC) with 95% confidence intervals (CIs). The AUC value in the sROC curve was used to evaluate the diagnostic efficacy of the test, with values ranging from 0.5-0.7, 0.7-0.9, and 0.9-1.0 indicating low, moderate, and high efficacy, respectively. We further explored the threshold effect based on Spearman's correlation coefficient and P value through Meta-DiSc 1.4 software. Heterogeneity between studies was assessed by Q-test and I² statistics, with I² values greater than 50% and P-values less than 0.05 considered significant heterogeneity, requiring selection of a random-effects model.

Subgroup analysis We conducted subgroup analysis and regression analysis to explore the potential heterogeneity, grouped according to miRNA profiling, comparison type, sample size, miRNA expression, ethnicity and cut-off values setting.

Sensitivity analysis: To evaluate the stability of our results, we perform sensitivity analyses that analysis the overall outcome after removing individual study one by one.

Country(ies) involved China.

Keywords thyroid carcinoma, circulating miRNAs, biomarkers, diagnosis, meta-analysis.

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