Int J Clin Exp Med 2018;11(3):1475-1482
www.ijcem.com /ISSN:1940-5901/IJCEM0063156

Review Article

Potential diagnostic role of miRNA-106a in gastric cancer: a meta analysis

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Received May 20, 2017; Accepted February 6, 2018; Epub March 15, 2018; Published March 30, 2018

Abstract: Background: Mounting studies report that microRNAs may be useful as diagnostic biomarkers of gastric cancer (GC), and compared with healthy individuals, gastric cancer patients tend to have a significantly high concentration of microRNA-106a (miR-106a) in plasma. Accordingly, this meta-analysis aims to evaluate the potential diagnostic role of miR-106a in gastric cancer. Methods: PubMed, Embase, Web of Science and the Cochrane Library were searched for publications, which are related to the diagnostic role of miR-106a in gastric cancer. Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used to estimate the quality of all the studies. Then, the data of each qualified study were extracted to perform meta-analysis. The overall test performance was checked by the Receiver operating characteristic curves (ROC). And the Chi-square and I^2 test were used to assess the existence of heterogeneity. Results: Four studies involving 238 GC patients and 139 controls were included in our meta-analysis. The results indicated that the pooled sensitivity and specificity are 71.6% (95% confidence interval (CI): 59.6%-81.2%) and79.2% (95% CI: 55.3%-92.1%) respectively. Furthermore, the value of AUC (area under the summary ROC curve) is 0.79. Conclusion: This meta-analysis indicates that miR-106a has a moderate sensitivity and specificity in the diagnosis of GC. In order to improve the accuracy of diagnosis, more large-scale studies about the role of miR-106a are required.

Keywords: MicroRNA-106a, gastric cancer, diagnosis, meta-analysis

Introduction

Gastric cancer is one of the most common gastrointestinal malignancies; the rates of incidence and death of GC are still ranked fourth and second in the global, though the incidence and mortality in some regions around the world are decreased over recent years [1, 2]. Most patients have been in the advanced stage and enduring a poor prognosis when confirmed GC, furthermore, there is no chance to treat with a radical surgery [3]. According to the research, early gastric cancer patients tend to have better prognosis with a 5-year survival rate of more than 90% [4]. Therefore, early diagnosis of GC can effectively improve the survival rate and decrease the mortality of patients. Currently, Endoscopic techniques have a significant value in the diagnosis of early gastric cancer; however, Endoscopy, a kind of invasive inspection, is not suitable for large-scale screening of GC, and it also has the characteristics of poor compliance and higher cost [5]. Therefore, there is a necessary to find a simple and effective method for the early diagnosis of gastric cancer.

Increasing evidences indicate that circulating MicroRNAs (miRNAs) can be acted as novel and non-invasive biomarkers in cancer diagnosis [6-9]. miRNAs are a large family of non-coding and single chain RNA that are about 19-23 nucleotides in length and encoded by endogenous genes, they regulate the target genes expression via binding to their 3'-untranslated region (3'UTR) of relevant mRNA [10-12]. miRNAs which can exist in serum and plasma solidly are related with the tumorigenesis and development of cancers closely [13]. Studies have found that miRNAs are expressed differentially between GC and normal gastric samples, indicating that they can act as novel biomarkers in the diagnosis of GC [14-16].

MicroRNA-106a (miR-106a) has been reported to work as an oncogene in GC tumorigenesis by

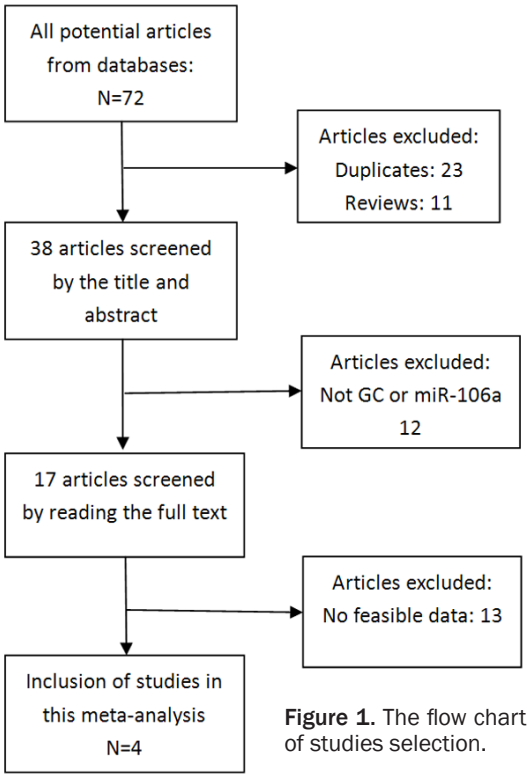

Figure 1. The flow chart of studies selection.

several studies. Furthermore, compared with normal gastric tissues, the serum level of miR-106a in GC is higher, and it facilitates the growth and metastasis of tumor cell [17-19]. All the results show that miR-106a is concerned with the tumorigenesis and progression of GC, and it may serve as an effective biomarker in the early diagnosis of GC.

In consideration of the current situation that there are different results of miR-106a in the diagnosis of GC reported by different studies, and whether it may act as a novel GC diagnosis method need to be confirmed, so is the accuracy of diagnosis. Therefore, we conduct this meta-analysis to systemically study and explore the potential role of miR-106a in the diagnosis of GC. To the best of our knowledge, this is the first study to focus upon the relation between miR-106a and diagnosis of GC.

Materials and methods

Selection of publications

We searched several databases including Pubmed, Embase and the Cochrane Library with the keywords “gastric” or “stomach” and “tumor” or “cancer” or “carcinoma” or “neoplasm” and “plasma” or “serum” or “serums” or “blood” and “microRNA-106a” or “miRNA-106a” or “miR-106a” up to February 28th. Two reviewers independently search and identify all of the publications, and a discussion is needed to reach consensus when meets with disagreements. Studies satisfy the following criteria are chosen: (1) the diagnosis of GC must be confirmed by histopathological examination, which is the gold standard of GC diagnosis; (2) the control group consists of healthy individual or patients with benign diseases; (3) the level of miR-106a must be detected from peripheral blood; (4) studies with detail data to calculate true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN). Furthermore, studies which are reviews, conference report, duplicate publications or lack of detail data to construct the two-by-two tables are excluded. All studies meet with the criteria above are included to conduct this meta-analysis.

Data extraction

Two reviewers (Z.C and S.Y-Y) independently extracted the revelation data from each included studies. Any controversial issue on a study was settled by team discussion until reaching consensus. The data are as follows: study characteristics (first author, the year and ethnicity of publications, case-control samples, and TNM staging details), TP, FP, TN and FN used for two-by-two tables.

Quality assessment

QUADAS-2 is the standard to assess the quality of each study’s diagnostic accuracy and it is used to evaluate the quality of included studies in this meta-analysis [20].

Statistical analysis

The software of Stata 12.0 and Meta-DiSc version 1.4 were chosen to perform the data analysis [21, 22]. The bivariate meta-analysis model was used to generate pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and the bivariate summary receiver operator characteristic (SROC) curve [23]. The area under the curve (AUC) of 1.0 indicates an ideal discriminatory ability [24]. The forest plots of sensitivity and specificity of miR-106a were depicted with the random effects approach. Spearman correlation coefficient, a calculated

Table 1. Characteristics of included studies and quality assessment.

First author	Year	Study design	Patients/controls	Stage I, II%	QUADAS2 scores	Sen%	Spe%	AUC	Cut-off	Method
Tsujiura [26]	2010	Case Control	69/30	73.9	6	76.8*	50.0*	0.634	0.014* amol/L	qRT-PCR
Hou [27]	2015	Case Control	80/60	56.3	5	77.5	93.8	0.895	3.65* 2-ΔΔCt	RT-PCR
Yuan [28]	2016	Case Control	48/22	45.83	5	77.1	63.6	0.828	2.55 2-ΔΔCt	qRT-PCR
Zhou [29]	2010	Case Control	41/27	NC	4	48.2	90.2	0.684	6.54 2-ΔΔCt	qRT-PCR

Note: *Calculated with offered data; AUC=Area under the curve of receiver operator curve; QUADAS 2=quality assessment for studies of diagnostic accuracy 2; NC=not clear; Sen=specificity; Spe=specificity.

result between the log value of sensitivity and 1-specificity, was chosen to evaluate the heterogeneity derived from threshold effect. The result of spearman correlation coefficient of 1 indicates that there is a significantly threshold effect. The heterogeneity of non-threshold effect was tested by indicators of Chi-square and I^2 test, a value of $P<0.05$ and $I^2>50\%$ show that the heterogeneity is existed [25]. Once there is a significant heterogeneity, meta-regression was performed to explore the likely sources. Besides, the Deeks' funnel plots were performed to test the publication bias.

Results

Included studies

Originally, 72 articles were obtained after searching from the database, of which 23 duplicated articles and 11 reviews were excluded. Then the remaining 38 articles were screened by reviewing abstract and the titles, as a result, 12 articles are not related with GC or miR-106a, and 9 articles are not the level in peripheral blood. After excluded, the left 17 articles were further screened by reading the full text, 13 are not diagnosis and without relevant data. Finally, 4 studies were eligible for this meta-analysis [26-29]. The **Figure 1** shows the flow chart of study screening.

Study characteristics and quality assessment

Totally, the 4 studies containing 238 GC and 139 controls were available in this analysis. All of the GC patients were confirmed by the gold standard, histopathologic diagnosis. Each study has a well-defined standard for tumor node metastasis(TNM), such as: IGCC/TNM staging system [26], TNM staging system (7^{th} version) by AJCC [29] and UICC [27], the International Union Against Cancer [28]. And the controls are all healthy volunteers without any malignant tumors. In these studies, the quantity of miR-106a in peripheral blood was detected by Real-Time polymerase chain reaction (RT-PCR). The levels of miR-106a were normalized by the 2-ΔΔCt method in 3 studies. The 4 studies' quality was scored by QUADAS-2, and all studies get a score between 4 and 6 which indicate that the studies have a high quality. The characteristics and QUADAS-2 scores of all included studies are reflected in **Table 1**. Moreover, several data (sensitivity, specificity and cut-off value) were acquired by contacting authors in Tsujiura's [26] and Hou's [27] study.

Data analysis

The I^2 of heterogeneity in sensitivity and specificity are 77.81% and 88.43% respectively, which shows significant heterogeneity (**Figure 2**). Therefore, the random effects model was applied to this study. The pooled sensitivity of miR-106a for GC diagnosis is 71.6% (95% CI: 59.6%-81.2%) and the pooled specificity is 79.2% (95% CI: 55.3%-92.1%). The SROC curve with the AUC value of 0.79 is shown in **Figure 3**, which suggesting a moderate diagnostic accuracy. In addition, the combined PLR is 3.33 (95% CI: 1.32-8.41), the NLR is 0.39 (95% CI: 0.25-0.62) and DOR is 9.00 (95% CI: 2.75-29.45) in our analysis, indicating that the capacity of miR-106a distinguishing GC patients from healthy individual is moderate (**Figure 4**).

Heterogeneity analysis

The heterogeneity of diagnosis meta-analysis derives from threshold effect and non-threshold effect. The I^2 of heterogeneity test is 87.25% and shows a significant heterogeneity.

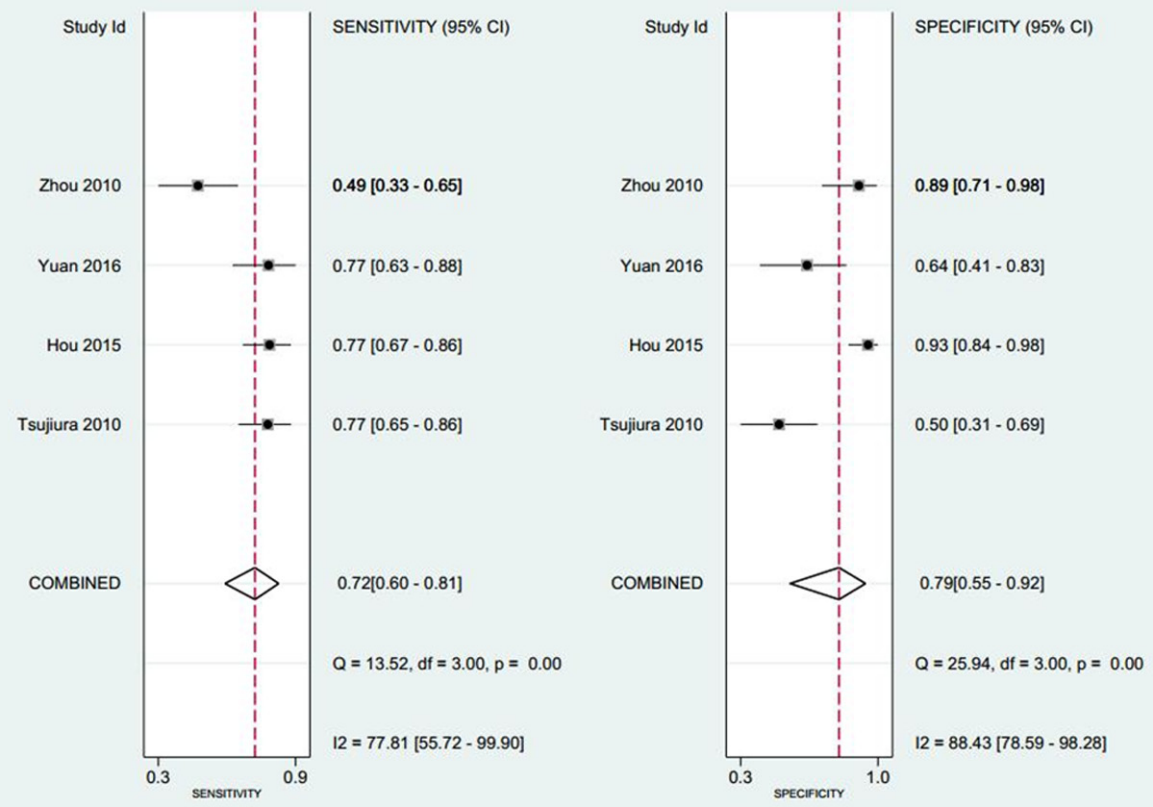

Figure 2. Forest plots of sensitivities and specificities from test accuracy studies of miR-106a in the diagnosis of GC.

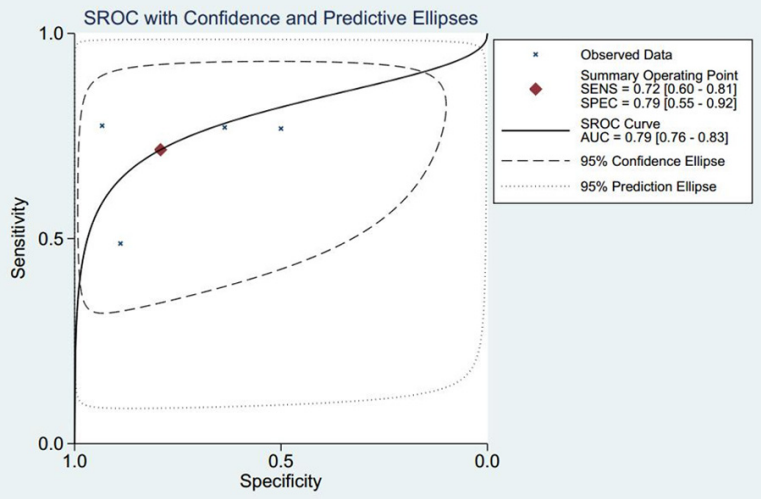

Figure 3. Summary receiver operating characteristic curves of miR-106a in the diagnosis of GC.

Spearman correlation coefficient was used to analyze the threshold effect in this meta-analysis. As a result, the Spearman value is -0.4 (P=0.6) which implies that threshold effect does not cause heterogeneity. Accordingly, meta-regression analysis was performed to explore the potential sources of heterogeneity. The analysis indicates that neither ethic background, percentage of TNM staging (stage I, II %) nor detection method causes the heterogeneity (**Table 2**).

Then, Sensitivity analysis was performed to explore the origin of heterogeneity and it showed that individual study can influence the results of meta-analysis significantly. When the data of Hou's study was deleted, the heterogeneity analysis demonstrates that there is no heterogeneity between the rest 3 studies. The value of chi-squared is 1.23 (p=0.540) and I^2 is 0.0%. However, the pooled DOR of the remaining studies was 4.752 which was decreased (**Table 3**).

Publication bias

A funnel plot was used to assess the publication bias in our study (**Figure 5**). The *P*-value of

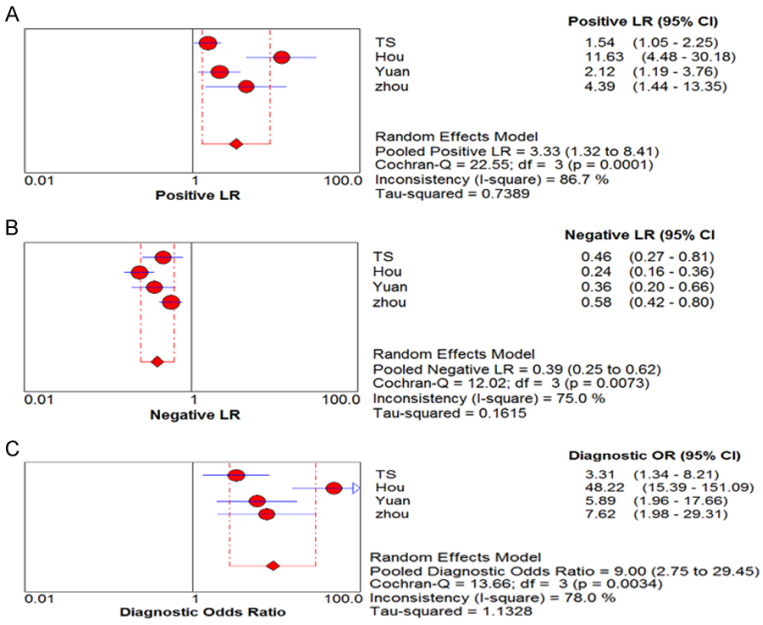

Figure 4. The combined PLR, NLR and DOR of miR-106a in the diagnosis of GC.

Table 2. The results of meta-regression to source the heterogeneity

Variable	Coefficient	Std	*P*-value	RDOR
Country	-0.704	2.2725	0.8087	0.49
Method	-1.935	0.7860	0.2456	0.14
Stage I II %	-0.704	2.2725	0.8087	0.49

Note: RDOR, relative DOR; P>0.05 represents no heterogeneity.

Table 3. Heterogeneity analysis of rest 3 studies (Random effects model)

Study	DOR	95% (CI)	Weight (%)	Chi-squared	*P* value
Tsujiura [26]	3.313	1.336-8.214	46.79		
Yuan [28]	5.886	1.962-17.665	31.96		
Zhou [29]	7.619	1.980-29.314	21.26		
Pooled DOR	4.752	2.553-8.844	100	1.23	0.540

linear regression method is 0.178 (P>0.1), which shows that there is no publication bias. As a result of the limited number of included studies, the funnel plot shows a degree of asymmetry. Therefore, whether there exists a publication bias in the meta-analysis is still uncertain.

Discussion

The different tumor stages have a different impact on the 5-year overall survival rate of gastric cancer, patients with stage I had a 5-year survival rate over 90%, while stage IV patients had a less than 5% 5-year survival rate [30, 31]. Therefore, early diagnosis is an effective method to improve the prognosis of GC patients. Obviously, endoscopic examination which is a kind of invasive method is not suitable for screening in large-scale. Increasing studies have been focusing on the new method of early diagnosis of GC [32-35]. The plasma level of miR-106a in GC is reported to be overexpressed in more and more studies [26-29, 36]. As far as we are concerned, this study is the first meta-analysis to explore the potential value of miR-106a in the diagnosis of GC.

The result of this meta-analysis indicates that miR-106a has a satisfactory accuracy of diagnosis. The pooled sensitivity and specificity are 71.6% and 79.2% respectively, and the value of AUC calculated from SROC is 0.79. The diagnostic odds ratio (DOR) which is ranged from 0 to infinity is used to estimate the ability of miR-106a in discriminating GC patients from non GC individuals. A higher value means a better discriminatory ability. Therefore, the AUC of 0.79 and the DOR value of 9.61 shows that miR-106a is a better biomarker in diagnosing GC. Furthermore, compared to the traditional serum biomarker CA19-9 and CEA, miR-106a has a higher sensitivity and specificity [37].

Currently, the biomarkers used for cancer diagnosis are mostly non-specific, the detection of a single biomarker has the characteristics of low positive rate and poor sensitivity. Therefore, the combination detection of several biomarkers is likely to be an effective and promising method for cancer diagnosis. Chen et al report-

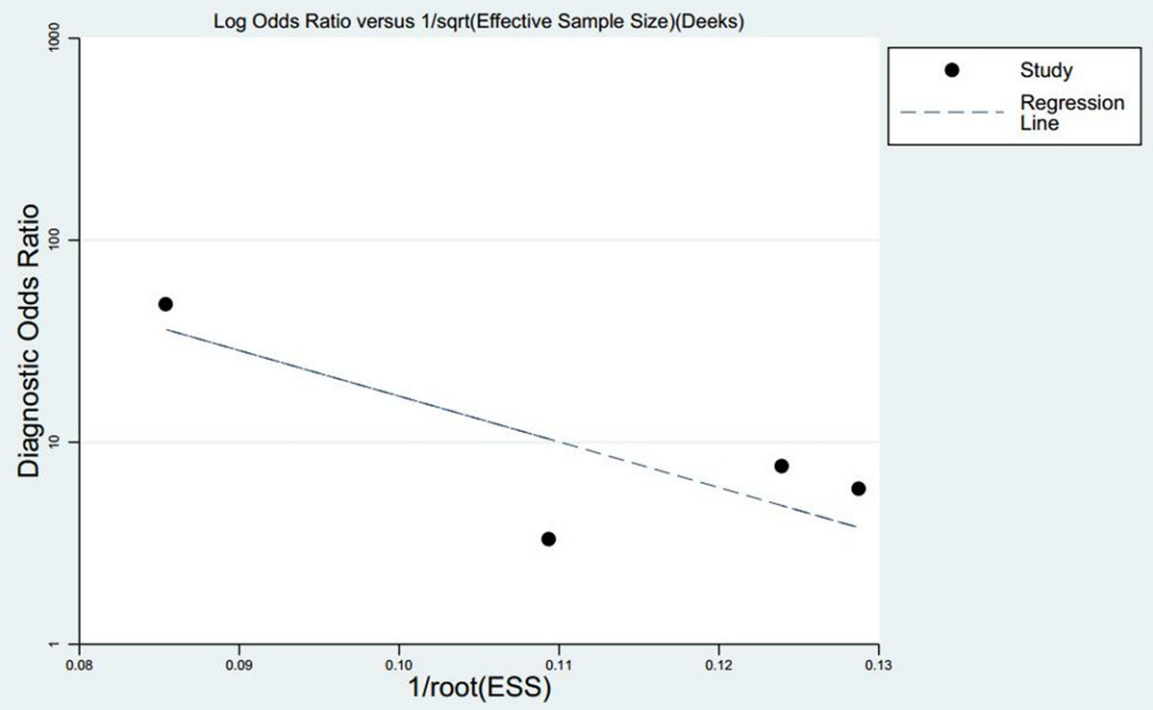

Figure 5. Funnel plot for the publication bias of included studies.

ed that the combination biomarkers mir-181a-1/KAT2B have a sensitivity of 95.83% and specificity of 94.12%, and they could be used as an independent diagnostic indicator for GC patients [38]. Besides, the detection of a panel of miRNAs also presented a high diagnostic accuracy for the early-stage GC [39]. Accordingly, this meta-analysis indicates that the further study can focus on the combination detection of miR-106a and other biomarkers in the future.

However, this meta-analysis also has several drawbacks. Firstly, though there are more and more studies working on the role of miR-106a in diagnosing GC, our analysis included 4 studies and the study scale has a limitation. Secondly, there are no common standard for miRNA detection and no unified cut-off value in these studies, so the data supplied may exert a difference. Thirdly, the funnel plot shows that it has no publication bias, but the 4 studies are from China and Japan, which implies that the result of our study is limited, besides, the fewer number of controls may have an influence on publication bias. Fourthly, although we try the best to contact with authors for the independent patient data, we fail to acquire the numbers of different tumor stages, as a result that we can't perform subgroup analysis to seek for the potential source of heterogeneity.

In conclusion, the sensitivity and specificity of miR-106a in diagnosing GC is moderate. The more and larger studies are needed in the future to improve the diagnostic accuracy.

Disclosure of conflict of interest

None.

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