REVIEW

Diagnostic accuracy of circulating microRNA in hepatitis B virus-related hepatocellular carcinoma: a meta-analysis based on Asian data

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ABSTRACT

Background and aim: hepatitis B virus (HBV) is the main risk factor for hepatocellular carcinoma (HCC). We performed a meta-analysis based on Asian data to evaluate the diagnostic accuracy of circulating microRNA as a non-invasive biomarker in the diagnosis of HBV-related HCC.

Methods: a comprehensive literature search (updated to May 12, 2021) in PubMed, Embase, Web of Science, Wanfang Database, and China National Knowledge Infrastructure (CNKI) was performed to identify eligible studies. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) for diagnosing HBV-related HCC were pooled in this meta-analysis. A subgroup analysis was performed to explore heterogeneity, and Deeks' funnel plot was used to assess publication bias.

Results: a total of 19 articles including 32 studies were included in the current meta-analysis. The overall sensitivity, specificity, PLR, NLR, DOR and AUC were 0.83 (95 % CI: 0.79 to 0.87), 0.78 (95 % CI: 0.73 to 0.83), 3.9 (95 % CI: 3.0 to 4.9), 0.21 (95 % CI: 0.16 to 0.27), 18 (95 % CI: 12 to 27) and 0.88 (95 % CI: 0.85 to 0.91), respectively. Subgroup analysis shows that miRNA clusters with a large sample size showed better diagnostic accuracy. Although there is no publication bias, the research still has some limitations.

Conclusions: circulating miRNAs could serve as a potential non-invasive biomarker in diagnosing HBV-related HCC in Asian populations.

Keywords: Hepatocellular carcinoma. Hepatitis B virus. MicroRNA. Biomarkers. Meta-analysis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of deaths globally (1). Its main risk factor is hepatitis B virus (HBV) infection, which accounts for approximately 50 % of HCC cases and almost all liver cancers in childhood (2). The majority of HBV-related HCC cases worldwide occur in the Asia-Pacific region. Unfortunately, early HCC is generally asymptomatic and the tumor progresses rapidly. The tumor is often found after metastasis have occurred, a time when it cannot be locally ablated or surgically removed, causing a high mortality rate. The diagnosis of HCC usually relies on radiological imaging techniques (such as ultrasound, CT, and MRI) in combination with AFP dosing and histological analysis of liver biopsies. Although the imaging method is non-invasive, it cannot detect small lesions due to its low sensitivity (3). Alpha-fetoprotein (AFP) is a standard serum biomarker for the diagnosis of HCC, and its higher level of expression is closely related to the clinicopathological characteristics

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of patients with HCC (4). Although AFP has been widely used in the clinical diagnosis and prognostic monitoring of HCC, it has limited sensitivity and specificity. Some liver nodules may not release AFP, and patients with active chronic hepatitis or liver cirrhosis may have high levels of AFP (5). Liver biopsy, the gold standard for the diagnosis and stage assessment of HCC, depends on tumor size and cirrhosis status. Due to its invasive nature, various complications, insufficient sampling, and interpretation variability the application of liver biopsy to the management of HCC is limited. More powerful biomarkers are needed to compensate for the shortcomings that existing diagnostic tools have for the detection of HCC.

Circulating microRNA (miRNA) has been widely used in recent years in different cancer clinical settings, including early detection, prediction, monitoring of disease progression, and response to treatment (6). A recent meta-analysis showed that circulating miR-122 can be used as a diagnostic marker for HCC (7). In addition, miRNA plays a crucial role in HBV-associated hepato-carcinogenesis. They can act as tumor suppressors by negatively regulating the expression of oncogenes or as tumor promoters by limiting the expression of onco-suppressor proteins, depending on the cellular function of the target genes (6). Several studies reported on the possibility of using miRNA as a non-invasive biomarker for HBV-related HCC, and their results were satisfactory but inconsistent. Therefore, this meta-analysis aims to evaluate the diagnostic value of circulating miRNA as a non-invasive biomarker for the diagnosis of HBV-related HCC.

MATERIALS AND METHODS

Search strategy and literature selection

This meta-analysis was performed according to the PRISMA statement (8). Two investigators independently conducted a comprehensive search of PubMed, Embase, Web of Science, Wanfang Database, and China National Knowledge Infrastructure (CNKI) up to May 12, 2021. MeSH keywords and terms were used, and search terms were as follows: "hepatocellular carcinoma" or "liver cancer" or "HCC" and "microRNA" or "miRNA" or "miR" and "hepatitis b virus" or "HBV" or "chronic hepatitis". The searches were limited to publications with human subjects, without language restrictions. A manual search was performed using the references listed in the original articles and review articles retrieved.

Inclusion and exclusion criteria

We screened the literature according to the inclusion criteria: 1) clinical studies aimed to assess the diagnostic accuracy of circulating miRNAs for the diagnosis of HBV-related HCC; all patients were diagnosed by means of histopathology examinations; 2) the control group was composed of HBV-infected individuals without HCC, including chronic hepatitis B (CHB) and HBV-related liver cirrhosis (LC); 3) all HBV-related HCC cases had received no treatment (surgery, radiotherapy, or chemotherapy) before being collected; 4) the miRNAs obtained were measured in serum or plasma samples; 5) the studies contained sufficient data on sensitivity, specificity, and sample size to construct a two-by-two diagnostic table. In contrast, the exclusion criteria were: 1) duplicate reports or publications with incomplete information; 2) miRNAs obtained from cell lines, animals, liver tissue, or urine; 3) comments, reviews, case reports, letters to the editors, and 4) systematic reviews or meta-analyses.

Data extraction and quality assessment

Relevant studies were selected based on title, abstract, and full text, which were reviewed for further assessment if the study was collected by one of the two investigators. We extracted the following data from each eligible study: first author's name, publication year, miRNA profile, regulation mode, sample size, specimen source, relevant statistical data required, and methodological quality information. In addition, we assessed the quality of the included studies using the Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool (9). A third investigator resolved any disagreements.

Statistical analysis

The number of true positives, false positives, false negatives, and true negatives among patients in each study was extracted. Heterogeneity was assessed using I^2 statistics. Significant heterogeneity was indicated by an I^2 value greater than 50 %, and then a random-effects model was performed. The potential sources of heterogeneity were explored by subgroup analysis. We calculated sensitivity (SEN), specificity (SPE), the positive likelihood ratio (PLR), the negative likelihood ratio (NLR), and the diagnostic odds ratio (DOR). Besides, we generated the summary receiver operating characteristics (SROC) curve and calculated the area under the SROC curve (AUC) for both the overall and subgroup analyses. Assessment criteria for diagnostic efficacy included: AUC = 1.00 is perfect, AUC > 0.90 is excellent, AUC > 0.80 is good, AUC < 0.80 is medium (10). Finally, we assessed the potential publication bias by using Deeks' funnel plot asymmetry test, in which $p < 0.05$ indicated statistical significance. All statistical analyses were performed using Review Manager 5.2 and STATA version 13.0.

RESULTS

Study selection and literature characteristics

As shown in figure 1, the flow chart of the article selection process, a total of 3764 articles were initially identified from the primary literature search strategy, of which 818 were from PubMed, 1792 were from Embase, 887 were from Web of Science, 120 were from the Wan-fang Databases, and 147 were from Chinese National Knowledge Infrastructure (CKNI). A total of 3117 articles were left for screening after 647 duplicates were removed. After reviewing titles and abstracts manually, 3055 articles were excluded because they reported irrelevant studies, animal experiments or cell line studies, or were review articles or letters. Subsequently, the full texts of the remaining 62 articles were read to assess eligibility, and 43 articles were excluded. Finally, 32 studies from 19 articles (11-29) were included in the current meta-analysis.

The main characteristics of the 19 articles included are summarized in table 1, in order by year of publication,

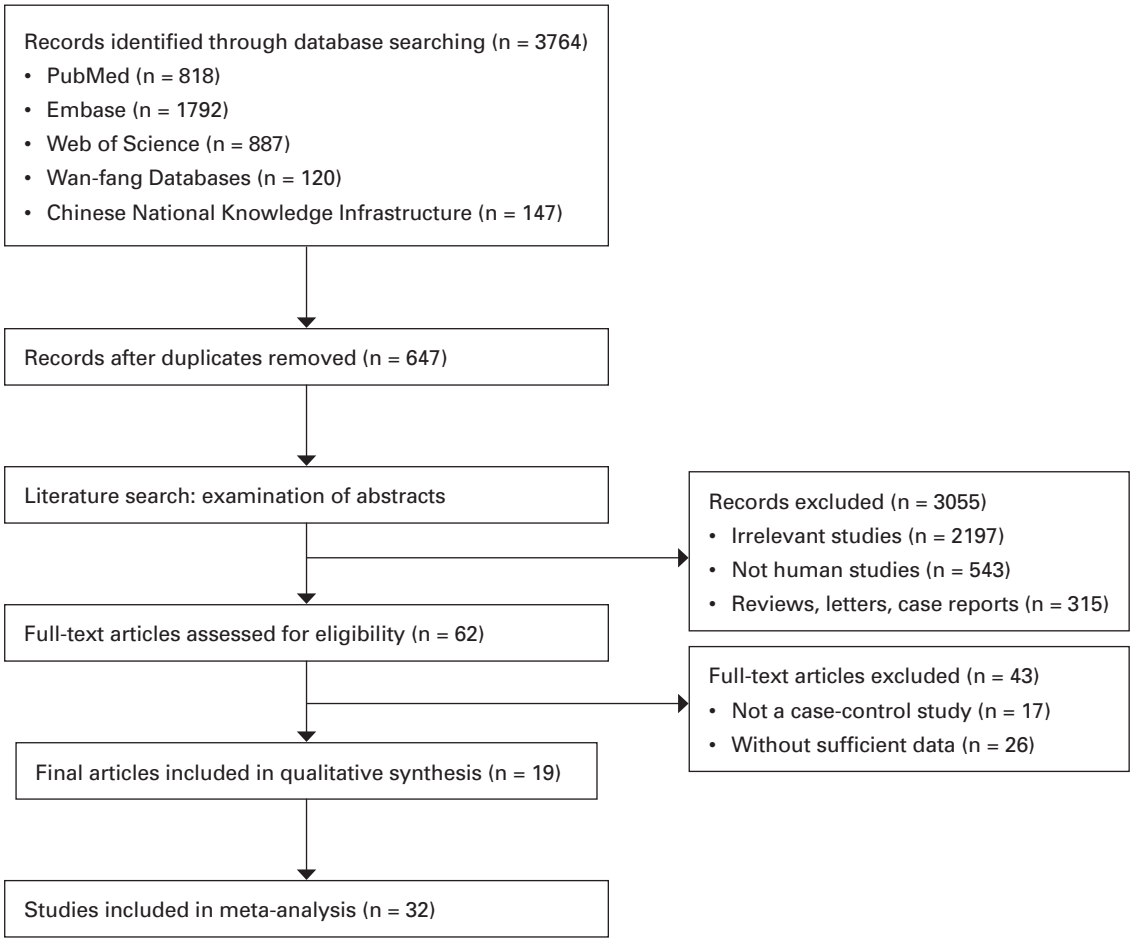

Fig. 1. *The flow chart of this meta-analysis to identify inclusion studies.*

ranging from 2010 to 2021. In total, 2590 HBV-related HCC patients and 1963 controls were included. In total also, 15 articles referred to a single miRNAs, and four articles focused on miRNA clusters. In addition, real-time quantitative reverse transcription PCR (qRT-PCR) was used to detect miRNA expression levels in 15 serum and four plasma specimens. Most of the studies came from China, and the dominant ethnicity of the study subjects was Asian. The methodological quality assessment graph is shown in figure 2.

Diagnostic accuracy of circulating miRNAs in HBV-related HCC

The sensitivities and specificities of miRNAs in 32 studies that included 2590 patients with HBV-related HCC and 1963 controls (CHB and HBV-related LC) were analyzed using a forest plot. There was significant heterogeneity among studies overall (I^2 = 83.25 % for sensitivity and I^2 = 82.34 % for specificity), and therefore a random-effects model was selected in our meta-analysis. Pooled results were as follows: sensitivity, 0.83 (95 % CI: 0.79 to 0.87); specificity, 0.78 (95 % CI: 0.73 to 0.83); PLR, 3.9 (95 % CI: 3.0 to 4.9); NLR, 0.21 (95 % CI: 0.16 to 0.27); DOR, 18 (95 % CI: 12 to 27), and AUC, 0.88 (95 % CI: 0.85 to 0.91) (Fig. 3). The results showed that circulating miRNAs had excellent diagnostic accuracy for HBV-related HCC.

Diagnostic value of miR-125b for HBV-related HCC

There were 6 studies accessing miR-125b as a diagnostic biomarker for HBV-related HCC, including 391 HBV-related HCC patients and 454 controls. The combined sensitivity was 0.89 (95 % CI: 0.82 to 0.94), specificity was 0.85 (95 % CI: 0.74 to 0.92), PLR was 5.5 (95 % CI: 3.9 to 9.9), NLR was 0.13 (95 % CI: 0.08 to 0.21), DOR was 47 (95 % CI: 26 to 83), and the AUC was 0.94 (95 % CI: 0.91 to 0.96) (Fig. 4).

Subgroup analysis

We conducted a subgroup analysis to find probable sources of heterogeneity, which was performed according to country, miRNA profiling, regulation mode, type of control, sample size, and specimen types. The detailed results of all subgroup analyses are summarized in table 2. We found that studies in a Chinese population showed a better diagnostic value when compared to those in other populations: sensitivity (0.85 vs. 0.64), specificity (0.80 vs. 0.71), PLR (4.2 vs. 2.2), NLR (0.19 vs. 0.51), DOR (22 vs. 4), and AUC (0.90 vs. 0.72). In all, miRNA clusters exhibited a better diagnostic value than single miRNAs: sensitivity (0.83 vs. 0.84), specificity (0.89 vs. 0.76), PLR (7.3 vs. 3.5), NLR (0.20 vs. 0.21), DOR (37 vs. 16), and AUC (0.91 vs. 0.87). Furthermore, the ability of miRNA to distinguish HBV-related HCC from HBV-related LC is better than for CHB:

Table 1. *Characteristics of the included studies*

Author	Year	Country	microRNAs	Regulation mode	Sample size				Specimen	Diagnostic power		
					Case	No.	Control	No.		Sen (%)	Spe (%)	AUC
Single miRNA												
Qi, P.	2011	China	miR-122	Up	HCC	70	CHB	48	Serum	0.78	0.58	0.63
Li, L.	2012	China	miR-18a	Up	HCC	101	CHB + LC	30	Serum	0.77	0.70	0.78
Xie, Y.	2014	China	miR-101	Down	HCC	67	LC	61	Serum	0.96	0.90	0.98
Yu, F.	2015	China	miR-150	Down	HCC	120	CHB	110	Serum	0.79	0.77	0.88
Chen, Y.	2015	China	miR-96	Up	HCC	104	CHB	100	Serum	0.78	0.75	0.80
Ghosh, A.	2016	Indian	miR-126	Up	HCC	49	CHB + LC	38	Plasma	0.63	0.58	0.67
Ghosh, A.	2016	Indian	miR-142-3p	Up	HCC	49	CHB + LC	38	Plasma	0.32	0.91	0.55
Xiong, F.	2016	China	miR-99a	Down	HCC	32	CHB	30	Serum	0.84	0.57	0.69
Xiong, F.	2016	China	miR-125b	Down	HCC	32	CHB	30	Serum	0.91	0.57	0.70
Xiong, F.	2016	China	miR-99a	Up	HCC	32	LC	30	Serum	0.97	0.56	0.70
Lin, L.	2016	China	miR-224	Up	HCC	122	CHB + LC	135	Serum	0.87	0.71	0.84
Lin, L.	2016	China	miR-224	Up	HCC	122	LC	61	Serum	0.87	0.67	0.83
Lin, L.	2016	China	miR-224	Up	HCC	122	CHB	74	Serum	0.87	0.75	0.85
Chen, S.	2017	China	miR-125b	Down	HCC	64	CHB	63	Plasma	0.94	0.86	0.96
Chen, S.	2017	China	miR-125b	Down	HCC	64	LC	59	Plasma	0.89	0.88	0.96
Chen, S.	2017	China	miR-125b	Down	HCC	31	CHB + LC	102	Plasma	1.00	0.76	0.94
Zhao, Q.	2018	China	miR-143	Down	HCC	85	CHB	50	Serum	0.78	0.86	0.81
Zhao, Q.	2018	China	miR-145	Down	HCC	85	CHB	50	Serum	0.88	0.78	0.85
Xu, LJ.	2018	China	miR-125b	Up	HCC	100	CHB	100	Serum	0.81	0.87	0.80
Xu, LJ.	2018	China	miR-125b	Up	HCC	100	LC	100	Serum	0.78	0.96	0.91
Moradi, N.	2019	Iran	miR-214	Down	HCC	23	CHB	25	Plasma	0.85	0.43	0.52
Moradi, N.	2019	Iran	miR-6510	Down	HCC	23	CHB	25	Plasma	0.81	0.39	0.53
Moradi, N.	2019	Iran	miR-5193	Down	HCC	23	CHB	25	Plasma	0.80	0.82	0.82
Moradi, N.	2019	Iran	miR-34a	Down	HCC	23	CHB	25	Plasma	0.40	0.87	0.62
Zhang, W.	2020	China	miR-375	Down	HCC	63	CHB	74	Serum	0.94	0.64	0.77
Cao, X.	2020	China	miR-487b	Up	HCC	87	CHB	68	Serum	0.76	0.90	0.86
Li, X.	2021	China	miR-487b	Up	HCC	116	CHB	66	Serum	0.84	0.67	0.82
miRNA clusters												
Li, LM.	2010	China	miRNA clusters	Down	HCC	65	CHB	75	Serum	0.96	0.99	0.99
Zhou, J.	2011	China	miRNA clusters	Up	HCC	196	CHB	72	Plasma	0.79	0.76	0.84
Zhou, J.	2011	China	miRNA clusters	Up	HCC	196	LC	56	Plasma	0.75	0.91	0.88
Tan, Y.	2014	China	miRNA clusters	Up	HCC	103	LC	78	Serum	0.82	0.85	0.89
Zhu, HT.	2017	China	miRNA clusters	Up	HCC	121	LC	63	Serum	0.79	0.79	0.86

HCC: hepatitis B virus-related hepatocellular carcinoma; CHB: chronic hepatitis B; LC: hepatitis B virus-related liver cirrhosis; Up: upregulated; Down: downregulated; Sen: sensitivity; Spe: specificity; AUC: area under the curve.

sensitivity (0.85 vs. 0.83), specificity (0.85 vs. 0.76), PLR (5.6 vs. 3.5), NLR (0.17 vs. 0.22), DOR (31 vs. 16), and AUC (0.91 vs. 0.87). On the other hand, studies with a sample size greater than 100 performed better: sensitivity (0.85 vs. 0.77), specificity (0.82 vs. 0.66), PLR (4.6 vs. 2.2), NLR (0.19 vs. 0.35), DOR (24 vs. 6), and AUC (0.90 vs. 0.77). Serum specimens had a slightly higher diagnostic value when compared to plasma: sensitivity (0.84 vs. 0.80), specificity (0.78 vs. 0.78), PLR (3.9 vs. 3.7), NLR (0.20 vs. 0.26), DOR (20 vs. 14), and AUC (0.89 vs. 0.86). Furthermore, down-regulated miRNAs have better diagnostic accuracy than up-regulated miRNAs: sensitivity (0.88 vs. 0.79), specificity (0.78 vs. 0.79), PLR (4.0 vs. 3.8), NLR (0.15 vs. 0.26), DOR (26 vs. 14), and AUC (0.91 vs. 0.86).

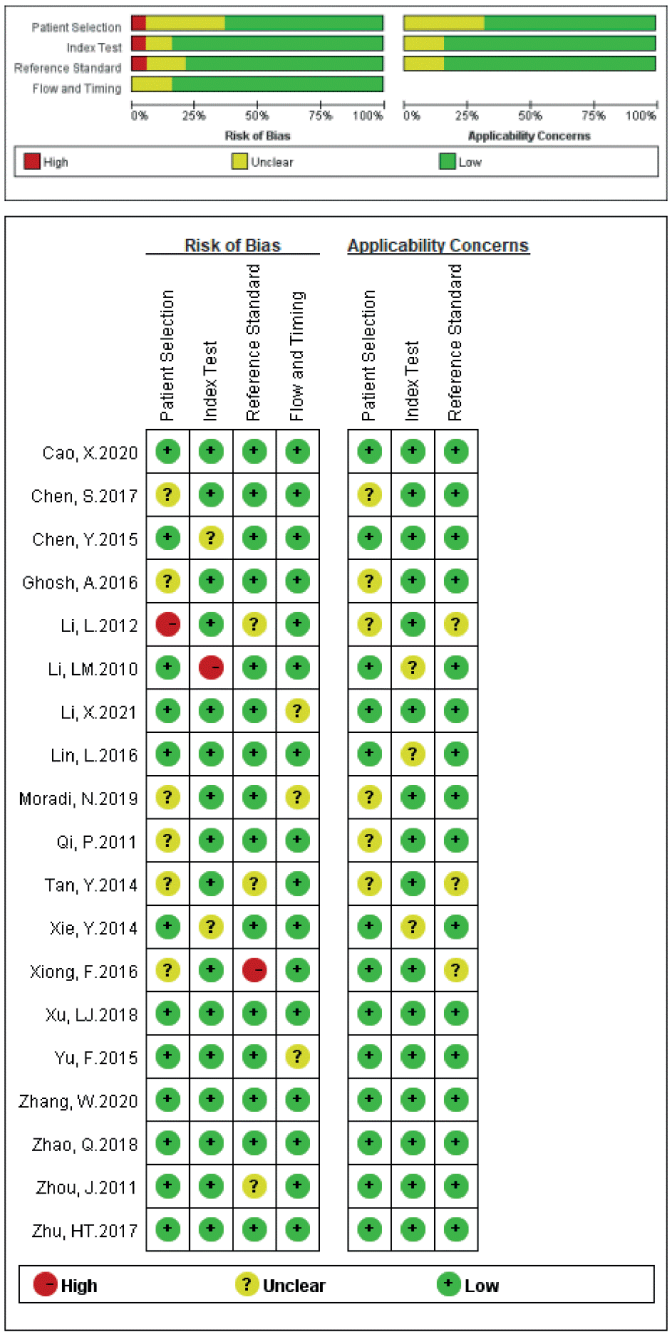

Fig. 2. *Quality evaluation according to the QUADAS-2 criteria.*

Publication bias

The publication bias of the included studies was verified using Deeks' funnel plot test. The pooled Deeks' test result for the overall study was P = 0.35 (Fig. 3D), and for miR-125b was P = 0.88 (Fig. 4D), indicating no significant publication bias in this meta-analysis.

DISCUSSION

HCC is one of the most prevalent malignant tumors worldwide, and chronic HBV infection continues to be one of the main causes of its pathogenesis. Several studies have reported the possibility of using miRNAs as non-invasive biomarkers for the diagnosis of HCC-HBV, but the results are inconsistent. Therefore, we performed this meta-analysis.

Multiple databases were searched, and finally 32 studies from 19 articles with 4553 patients (2590 HBV-related HCC subjects and 1963 controls) on the diagnostic value of circulating miRNAs for HBV-related HCC were included. In this meta-analysis, the pooled sensitivity was 0.83 (95 % CI: 0.79 to 0.87), and pooled specificity was 0.78 (95 % CI: 0.73 to 0.83); we also plotted the ROC curve and calculated the corresponding AUC, which was 0.88 (95 % CI: 0.85 to 0.91), which means that circulating miRNA has an excellent diagnostic precision for HBV-related HCC. We also calculated PLR, NLR, and DOR to test miRNAs discrimination ability, providing more meaningful references for clinical use. The combined PLR, NLR and DOR were 3.9 (95 % CI: 3.0 to 4.9), 0.21 (95 % CI: 0.16 to 0.27), and 18 (95 % CI: 12 to 27), respectively. This finding shows that the probability of a correct diagnosis of patients with HBV-related HCC is 18 times higher than that of a false negative diagnosis of controls. However, PLR is less than ten and NLR is greater than 0.1, which does not meet the general award criteria or exclusion decision (30). In addition, a recent meta-analysis also confirmed that circulating miRNAs showed promising potential for the diagnosis of HBV-related HCC patients with low AFP levels (31).

At the same time, we found that miR-125b had a higher diagnostic value for HBV-related HCC than other single miRNAs. It is reported that miR-125b plays an important role as an oncogene or tumor suppressor in HBV-related hepatocarcinogenesis and tumor progression (32). It can inhibit tumorigenesis by attacking Mcl-1 and IL-6R (33). Additionally, miR-125b suppresses hepatocyte migration and invasion by directly targeting the LIN28B oncogene and the transcriptional coactivator with the PDZ-binding motif (34). Moreover, miR-125b also inhibits cell proliferation, migration, and invasion in hepatocellular carcinoma by targeting thioredoxin reductase 1 (TXNRD1) (35). By monitoring the level of miR-125b in the blood, it may be possible to detect HBV infection with a higher risk of HCC in order to improve survival. Furthermore, Zheng and colleagues revealed that serum miR-125a-5p could be used as a non-invasive biomarker for monitoring liver disease progression (36).

A subgroup analysis was performed according to country, miRNA profiling, regulation mode, type of control, sample size, and specimen type to explore possible sources of heterogeneity among studies. It suggested that miRNA clusters had better diagnostic value than single miRNAs. A single miRNA lacks specificity because it not only detects cancer but also other infectious diseases, nonspecific inflammations, and acute lesions. In other words, miRNA clusters have more complex molecular mechanisms, such as competing endogenous RNA (ceRNAs) networks that intersect during tumorigenesis (such as the appearance and development of severe tumors), an association that may be valuable for the detection of HCC. Furthermore, we found that the ability of miRNA to distinguish HBV-related HCC from HBV-related LC is better than using another control group, which still requires large-scale prospective studies to consol-

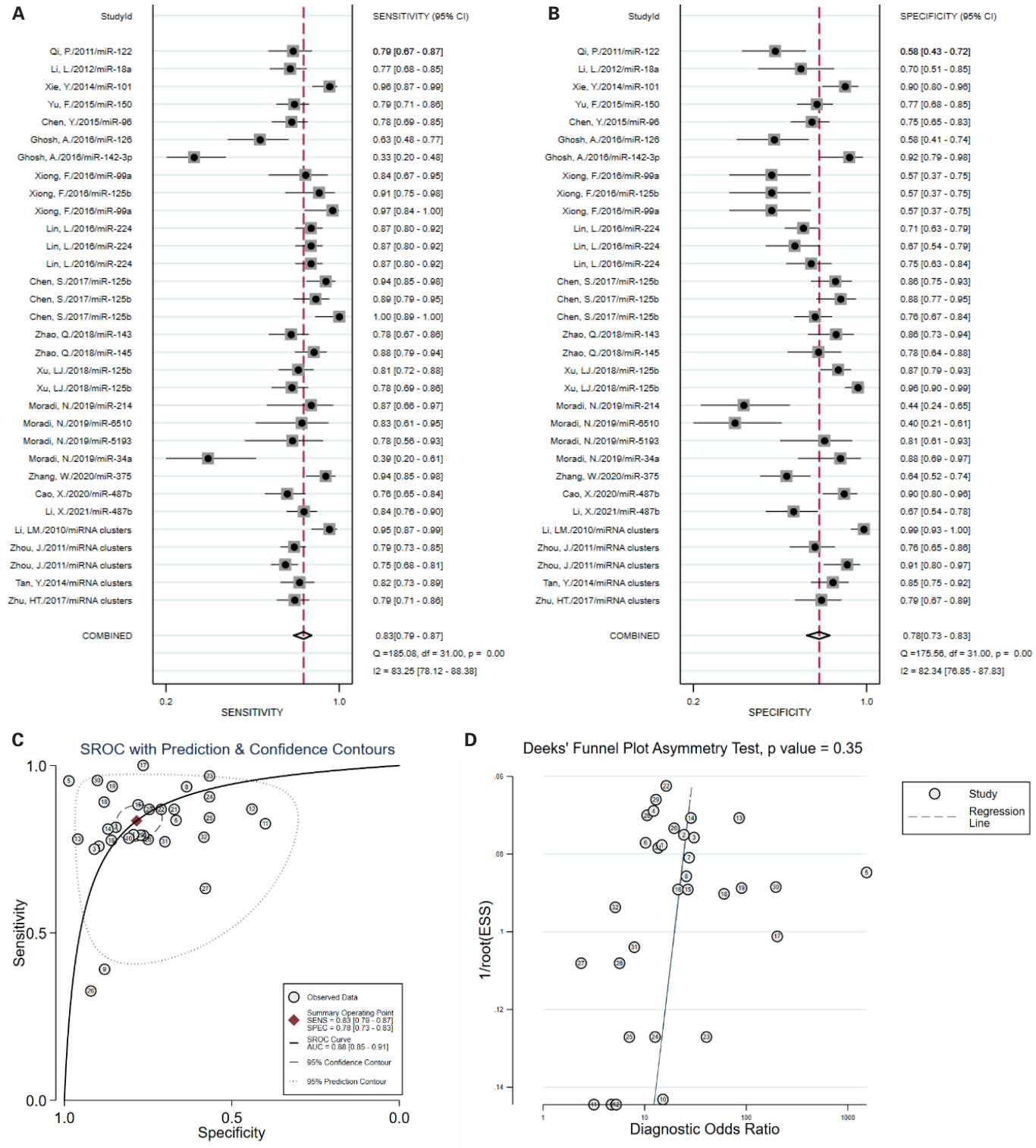

Fig. 3. *Forest plot of (A) sensitivity, (B) specificity, (C) area under the curve (AUC), and (D) Deeks' funnel plot of circulating miRNAs for diagnosing HBV-related HCC.*

idate the results. Other than that, the results with a sample size greater than 100 showed a better diagnostic accuracy when compared to studies with smaller ones, which supports the use of larger sample studies in the future.

This meta-analysis has several advantages. Compared to a previous meta-analysis (37), we include the miRNAs detected in the latest studies, and exhaustively evaluate the diagnostic efficacy of circulating miRNAs for HBV-related HCC. Furthermore, the included studies were selected based on strict inclusion and exclusion criteria. Although we have tried our best to avoid bias, there were still some limitations. First, several valuable studies may have been missed despite the comprehensive search strategy during

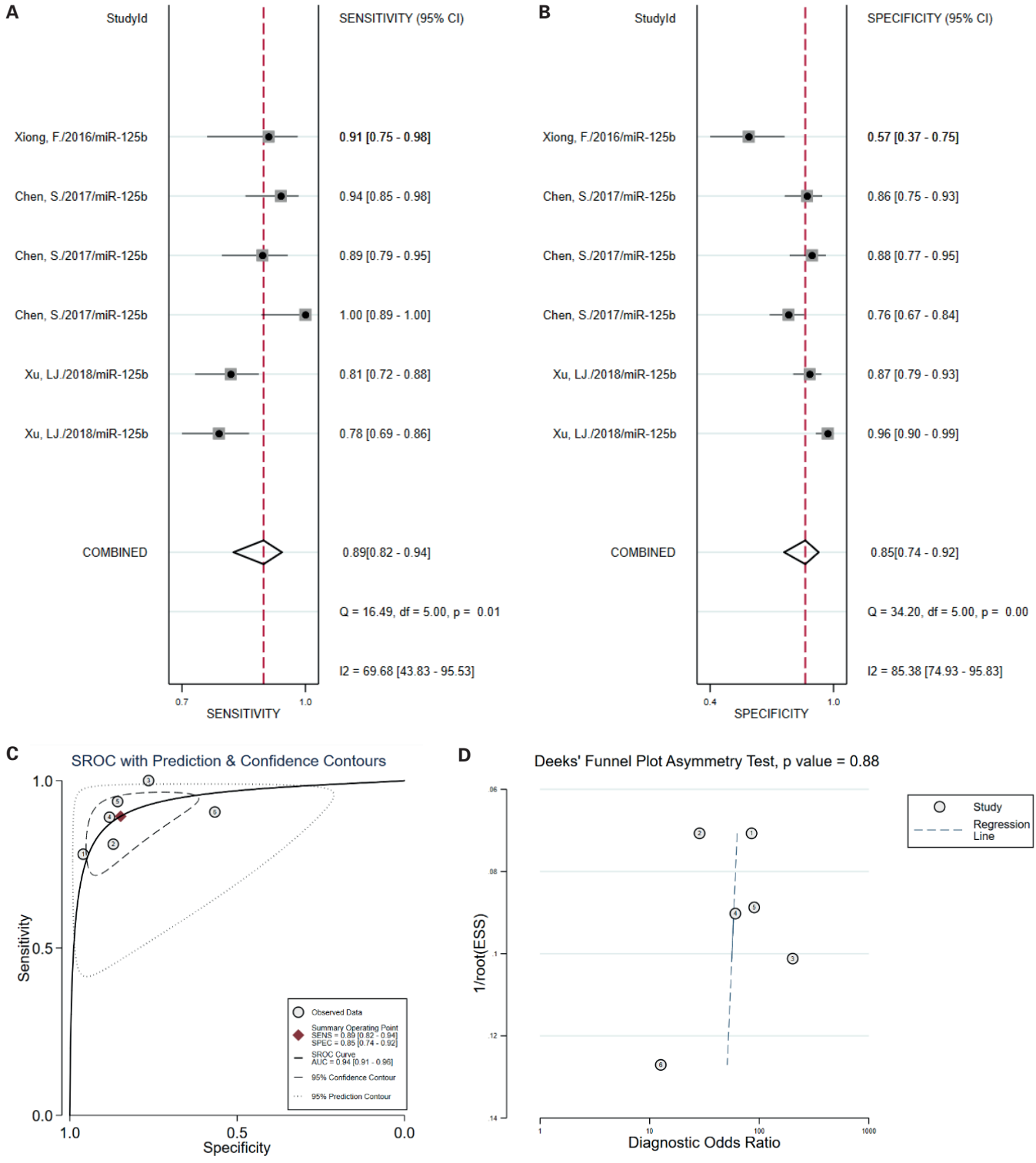

Fig. 4. *Forest plot of (A) sensitivity, (B) specificity, (C) area under the curve (AUC), and (D) Deeks' funnel plot of miR-125b for diagnosing HBV-related HCC.*

our literature search. Second, due to limited research data and differences in criteria, we did not extract cut-off values. Different cut-off values may lead to inconsistent conclusions. Third, a relatively small number of patients were included in the individual studies, thus limiting the strength of the conclusions of our meta-analysis. Fourth, it is important to determine the diagnostic value of miRNA in HBV-related HCC based on the size and characteristics of the tumor. Finally, all of the included studies were from Asia and mainly from China. The applicability of circulating miRNAs in other countries and regions still remains unknown. Therefore, a series of large-scale, multicenter, and multi-country clinical studies is needed to provide high-quality evidence.

Table 2. *Summary estimates of diagnostic power and their 95 % confidence intervals*

Subgroup	Sen (95 % CI)	Spe (95 % CI)	PLR (95 % CI)	NLR (95 % CI)	DOR (95 % CI)	AUC (95 % CI)
Country:						
China	0.85 (0.82-0.88)	0.80 (0.74-0.84)	4.2 (3.3-5.3)	0.19 (0.15-0.23)	22 (15-32)	0.90 (0.87-0.92)
Non-China	0.64 (0.45-0.80)	0.71 (0.49-0.86)	2.2 (1.4-3.4)	0.51 (0.36-0.71)	4 (3-7)	0.72 (0.68-0.76)
miRNA profiling:						
Single miRNA	0.84 (0.78-0.88)	0.76 (0.70-0.81)	3.5 (2.8-4.4)	0.21 (0.16-0.28)	16 (11-24)	0.87 (0.84-0.90)
miRNA clusters	0.83 (0.74-0.89)	0.89 (0.75-0.95)	7.3 (3.0-17.7)	0.20 (0.12-0.33)	37 (10-144)	0.91 (0.88-0.93)
Regulation mode:						
Up-regulated	0.79 (0.74-0.84)	0.79 (0.72-0.84)	3.8 (2.9-4.9)	0.26 (0.21-0.33)	14 (10-21)	0.86 (0.83-0.89)
Down-regulated	0.88 (0.82-0.93)	0.78 (0.68-0.86)	4.0 (2.6-6.1)	0.15 (0.09-0.24)	26 (12-57)	0.91 (0.88-0.93)
Control type:						
CHB	0.83 (0.79-0.87)	0.76 (0.68-0.83)	3.5 (2.6-4.8)	0.22 (0.17-0.28)	16 (10-26)	0.87 (0.84-0.90)
LC	0.85 (0.79-0.90)	0.85 (0.75-0.91)	5.6 (3.4-9.1)	0.17 (0.12-0.24)	31 (18-58)	0.91 (0.89-0.94)
CHB + LC	0.79 (0.49-0.94)	0.75 (0.64-0.83)	3.1 (2.1-4.7)	0.28 (0.10-0.81)	11 (3-42)	0.80 (0.77-0.84)
Sample size:						
< 100	0.77 (0.60-0.88)	0.66 (0.52-0.78)	2.2 (1.7-3.0)	0.35 (0.22-0.57)	6 (4-11)	0.77 (0.73-0.80)
≥ 100	0.85 (0.81-0.87)	0.82 (0.77-0.86)	4.6 (3.6-6.0)	0.19 (0.16-0.23)	24 (16-36)	0.90 (0.87-0.92)
Specimen type:						
Serum	0.84 (0.81-0.87)	0.78 (0.72-0.84)	3.9 (2.9-5.2)	0.20 (0.16-0.24)	20 (13-30)	0.89 (0.85-0.91)
Plasma	0.80 (0.65-0.89)	0.78 (0.67-0.87)	3.7 (2.4-5.7)	0.26 (0.15-0.46)	14 (6-32)	0.86 (0.82-0.88)

CHB: chronic hepatitis B; LC: hepatitis B virus-related liver cirrhosis; Sen: sensitivity; Spe: specificity; PLR: positive likelihood ratios; NLR: negative likelihood ratios; DOR: diagnostic odds ratio; AUC: area under the curve; CI: confidence interval.

CONCLUSION

In summary, circulating miRNAs could serve as a potential non-invasive biomarker for diagnosing HBV-related HCC in Asian populations. Additionally, using miRNA clusters and increasing sample size can improve diagnostic accuracy. In the future, large-scale multicenter clinical studies are still needed to verify our conclusions.

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