The Diagnostic and Prognostic Value of MiR-92a in Gastric Cancer

Hanxu Guo
Bengbu Medical College https://orcid.org/0000-0001-8004-7965
Yuhang Wang
Bengbu Medical College
Yongtian Li
Bengbu Medical College
Zishu Wang (zishuwang@163.com)

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Abstract

Background: miR-92a been proposed to have a significant role in the diagnosis andprognosis of different types of tumors, but the potential impact of its expression is still controversial due to the sample size. We conducted the meta-analysis to figure out whether miR-92a could be used as a detecting tool and prognosis of gastric cancer.

Method: A literature search was performedby retrieving Web ofScience, PubMed, EMBASE, ChineseNational Knowledge Infrastructure (CNKI), VIP(Technology of Chongqing databases) and Wanfang databases (last update by February2020). The sensitivity (SEN), specificity (SPE), positive and negative likelihood ratios (PLR and NLR), diagnostic odds ratio (DOR), and area under the ROC curve (AUC) were pooled to explore the diagnostic performance of miR-92a.The pooled HRs and 95%CIs of miR-92a for overall survival (OS) were calculated to explore the prognostic performance of miR-92a. Subgroup and meta-analysis were further carried out to explore the heterogeneity.

Results: 10 articles with12 studies were included. The pooled SEN and SPE were 0.76 (95% CI 0.64–0.85) and 0.79 (95% CI 0.63–0.90).Besides, the pooled PLR and NLR were3.7(95% CI 1.8–7.5)and 0.30 (95% CI 0.18–0.50), and the pooled DOR was 12(95% CI4–38). AUC was 0.84 (95% CI: 0.81–0.87), indicating asignificant value of miR-92a in the gastric cancer detection. For the prognostic analysis of miR-92a in gastric cancer, the univariate and multivariate data's poor OS were 1.46(95% CI0.87-2.45) and 1.46(95% CI0.90-2.39).

Conclusions: The present meta-analysis demonstrated that miR-92a could be a potential biomarker for thedetection of gastric cancer.Furthermore,high expression of miR-92a has a negative association with the survivalof patients, suggesting its potential as a prognostic indicator in gastric cancer.

Background

Gastric cancer, still represents the third common leading cause of cancer death with more than 1,000,000 cases in 2018 and an estimated 783,000 deaths (equating to 1 in every 12 deaths globally)[1]. Even now there are reports that conversion surgery following chemotherapy can improve survival[2], the clinical outcome of prognosis of gastric cancer patients is still poor. Due to the advanced stage when people are diagnosed with gastric cancer, a reliable biomarker is needed to diagnose gastric cancer and to indicate the survival time of patients, especially in the early stages.

MicroRNAs (miRNAs) refer to small and noncoding, which are actually involved at the post transcriptional level and bind to the 3 'UTR of their target messenger RNA (mRNA) to inhibit expression. And a large number of miRNAs have been down-regulated or up-regulated in human cancer, and regard as oncomiRs or oncosuppressor miRs [3]. More and more evidences show that miRNAs are involved in many biological processes including cell proliferation, apoptosis, differentiation, invasion and metastasis[4].In addition, a host of miRNAs in serum/plasma have been demonstrated to be a biomarker to identify gastric cancer at an early stage[5].miR-92a is a member of miR-17-5p and is associated with development of several cancers, including gastric cancer. Besides, miR-92a has been reported to be an important diagnostic and prognostic tool of other cancers, such as colorectal cancer[6], non-small cell lung cancer[7], breast cancer[8]etc. However, the particular clinical and prognostic roles of miR-92a in tumors still need to be identified more precisely.

Materials And Methods

Search strategy

To identify the relevant studies, we searched databases PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI), Technology of Chongqing(VIP) and Wan Fang databases (up to 10 Feb 2020).In each database, the keywords 'miRNA-92'or 'MicroRNA-92' or ' miR-92' or ' hsa-mir-92' or 'microRNA-92' were used as search terms together 'gastric cancer' or 'stomach neoplasm' or 'stomach cancer' or 'stomach carcinoma' or 'Stomach Neoplasms (Mesh)'. In

addition, we also sifted through the reference lists of original articles and manually searched from relevant reviews for additional literatures.

Inclusion and exclusion criteria

In order to screen out eligible studies, specific criteria were used: (1) gastric cancer was diagnosed via histopathology; (2) the study evaluated the diagnostic or prognostic value of miR-92a in gastric cancer; (3) sufficient data were provided to calculate the sensitivity and specificity(for diagnostic value)sufficient data were provided to calculate the HR and corresponding 95% CI(for prognostic value).

Exclusion criteria were as follows: laboratory studies, review articles, case reports, animal studies, or studies that did not provide sufficient data to calculate the diagnostic or prognostic value of miR-92a. If the same patient population was reported in several publications, the most recent study was selected for analysis.

Data Extraction

Two independent researchers extracted data from all the included studies (GHX and LYT), the uncertain results were assessed by another investigator (WYH). For the diagnostic value of miR-92a, the following data were extracted: (1)first author's name, country, year of publication, ethnicity of the population studied; (2)number of patients and controls;(3)assay type for evaluating miR-92a; (4)stage of gastric cancer; (5)diagnostic results of SEN, SPE, TP, FP, FN, and TN. For the prognostic value of miR-92a, the following data were extracted: (1)first author's name, country, year of publication, ethnicity of the population studied; (2)number of patients and controls;(3)assay type for evaluating miR-92a; (4)stage of gastric cancer; (5) prognostic outcomes including HRs of elevated miR-92a expression for OS/DFS.

Quality assessment

For diagnostic meta-analysis, we use QUADAS-2 as a tool to assess the quality of diagnostic value[9]. This tool includes four domains to evaluate: patient selection, index test, reference standard, and flow and timing through the study and timing of the index test and reference standard. The methodological quality graph and methodological quality summary were conducted by Review Manager (version 5.2. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2012). (Fig. 2) For prognostic meta-analysis, the quality of involved studies were evaluated with the Newcastle-Ottawa Scale (NOS)[10, 11].In addition, it can evaluate the quality of experiment by answering 8 questions. Each answer ranged score from 0 to 9. Two independent researcher extracted the data and assessed whether each included literature met the quality standards separately (GHX and LYT).

Statistical analysis

For diagnostic accuracy studies, the summary diagnostic index, including SEN and SPE, PLR, NLR, DOR with the corresponding 95% CIs, were calculated. Heterogeneity between studies was determined using Cochran's Q value and I^2 statistics. I^2 values < 25%, 25%-50%, and > 50% were set to indicate mild, moderate, and significant heterogeneity. If $I^2 > 50\%$, the random-effects model would be adopted. Otherwise, a fixed-effect model would be utilized for further analysis[12]. The summary receiver operating characteristic (SROC) curve was applied to assess the overall diagnostic accuracy, and the area under the SROC curve (AUC) were constructed for the diagnostic usefulness. Subgroup analysis was carried out by dividing the studies according to different by sample size, assay type and sample type.

For the prognostic meta-analyses, the pooled hazard ratio (HR) and its 95% CI were calculated to elucidate the link between high expression of miR-92a and corresponding OS of gastric cancer patients. Similarly, Cochran's Q test and I^2 statistics were applied to evaluate the heterogeneity of the pooled results[13]. All statistical analysis was performed by using Stata SE12.0 (StataCorp, College Station, TX) and RevMan5.3 software.

Results

Literature Search Results. The initial literature search elucidated a total of 181 articles. The identification and selection trial are briefly illustrated in Fig. 1. Of course, 172 articles were excluded because they did not meet our inclusion criteria. Eventually, this meta-analysis included 9 articles covering 12 cohort studies [14–23].

Characteristics and Quality assessment. For the diagnostic analysis, we included 8 studies of 498 cases and 819 controls (Table 1). Besides, the studies are divided by the amount of sample size. Gastric cancer was diagnosed using serum and plasma samples. In addition, all included studies detected miR-92a expression through qRT-PCR using different assay type (Taqman or SYBR). The quality of the included studies, evaluated by the QUADAS-2 assessment tool, is shown in Fig. 2a and 2b, which are suitable for quantitative synthesis.

Table 1
Characteristics of the studies that related to the diagnosis of gastric cancer.

Study	Country/Year	Design	Sample Type	Tumor/Control	Stage	Cut-off	Test Method	Sensitivity	Specificity
Zhang X	China/2011	R	Blood	80/40	I-IV	NA	RT-qPCR	85.7%	70.8%
Dong QG	China/2014	R	Blood	100/100	I-IV	NA	RT-qPCR	64.0%	82.0%
Liu CF	China/2019	R	Blood	45/89	I-II	NA	RT-qPCR	39.9%	97.8%
		R	Blood	125/89	III-IV	NA	RT-qPCR	39.3%	84.0%
Niu WW	China/2017	R	Blood	60/303	I-IV	NA	RT-qPCR	85.7%	70.8%
Li H	China/2014	R	Blood	79/38	I-IV	0.028	RT-qPCR	53.0%	84.0%
Zhu C	China/2014	R	Blood	40/40	I-IV	0.095	RT-qPCR	97.5%	85.0%
		R	Blood	48/102	I-IV	0.095	RT-qPCR	72.9%	73.5%

R: retrospective; QUADAS: quality assessment of diagnostic accuracy studies ; RT-qPCR: reverse transcription-quantitative polymerase chain reaction; NA, not available.

In 4 eligible studies for prognostic studies, 688 participants were included in the univariate analysis and 608 were included in the multivarite(Table 2).All studies were identified for assessing for OS.NOS are used for evaluating the detailed quality of these studies(Table 3).The NOS score range from 0 to 8.

Table 2
Characteristics of the studies that related to the prognosis of gastric cancer.

Study	Country/Year	Design	Sample Type	Number	Stage	Cut-off	Test Method	Outcome	HR(95%CI)
Wu Q	China/2013	R	Tissue	95	I-IV	NA	RT-qPCR	OS	(U)1.001(1.000-1.001) (M)1.001(1.000-1.001)
Peng W	China/2018	R	Blood	333	I-III	NA	RT-qPCR	OS DFS	(U)1.406(1.041–1.898) (M)1.353(0.972–1.885) (U)1.406(0.983–2.013) (M)1.309(0.882–1.944)
Ren C	China/2015	R	Tissue	180	I-IV	NA	Microarray	OS	(U)2.940(2.010–4.310) (M)3.340(1.670–6.700)

R: retrospective; QUADAS-2: quality assessment of diagnostic accuracy studies ; RT-qPCR: reverse transcription-quantitative polymerase chain reaction; NA, not available.; OS, Overall survival; DFS, Disease-free survival; HR, Hazard ratio; CI, Confidence interval.

Table 3
Newcastle–Ottawa quality assessments scale

First Author	Year	Quality indicators from Newcastle–Ottawa Scale								Score
		1	2	3	4	5	6	7	8	
Wu Q	2013	★	—	—	—	—	★	★	★	4
Ren C	2015	★	—	—	—	★	★	★	★	5
Peng W	2018	★	★	—	★	★★	★	★	—	7

1.Representativeness of the exposed cohort; 2. Selection of the non exposed cohort; 3. Ascertainment of exposure;4.Demonstration that outcome of interest was not present at start of study; 5. Comparability of cohorts on the basis of the design or analysis; 6. Assessment of outcome; 7. Was follow-up long enough for outcomes to occur; 8. Adequacy of follow up of cohorts.

Diagnosis meta-analysis

Diagnostic Value of miR-92a in Gastric cancer The summary results of the diagnostic indexes for miR-92a in gastric cancer are presented in Fig. 3. The pooled SEN and SPE were 0.76 (95% CI 0.64–0.85) and 0.79 (95% CI 0.63–0.90), and the pooled PLR and NLR were 3.7(95% CI 1.8–7.5) and 0.30 (95% CI 0.18–0.50) respectively.Meanwhile, the pooled DOR was 12 (95% CI 4–38). AUC was 0.84 (95% CI: 0.81–0.87) (Fig. 4). The results had significant heterogeneity (P < 0 01).

Gastric Cancer In order to annalyze the heterogeneity between studies, a subgroup was performed according to assay type, type of the sample and sample size. As the results shown in Table 4, there aren't any significantly differences in the the summary of sensitivity and specificity according to assay type, type of the sample and sample size.

Table 4
Subgroup analysis of the diagnostic value of miR-92a in gastric cancer.

	Subgroup	Sensitivity	P1	Specificity	P2
Sample Size	> 500	0.70 [0.54–0.86]	0.07	0.78 [0.59–0.98]	0.70
	< 500	0.82 [0.70–0.94]		0.81 [0.62–0.99]	
Assay Type	SYBR	0.77 [0.65–0.89]	0.79	0.73 [0.57–0.90]	0.08
	Taqman	0.74 [0.51–0.97]		0.93 [0.82–1.00]	
Sample Type	serum	0.74 [0.60–0.88]	0.24	0.73 [0.54–0.92]	0.16
	plasm	0.80 [0.64–0.95]		0.88 [0.74–1.00]	

Prognosis meta-analysis

Prognostic Value of miR-92a in Gastric cancer The univariate (I^2 = 91.6%) and multivariate data (I^2 = 86.4%) were analyzed separately using the Random effect model due to high heterogeneity in the data. The 4 studies included for univariate analysis showed that there was not significant correction between over-expression of miRNA-92a and poor OS (HR 1.46 95% CI 0.87–2.45) (Fig. 5). The 3 studies included for multivariate analysis showed there is not significant association between high expression of miR-92a and OS (HR 1.46 95% CI 0.90–2.39) (Fig. 6).

Sensitivity Analysis of the Prognostic Value of miR-92a Expression in Gastric Cancer In univariate analysis, Only one study [21] used the blood sample to investigate the association of miR-92a with OS. This study was omitted, and we found that the result remained similar to the overall results (HR 1.456 95%CI 0.620–3.416). In multivariate analysis, the study[21] that is still only one used palsma was excluded found that sensitivity result was in line with the overall results(HR 1.735 95% 0.54–5.63).

Discussion

Currently, qualifying the up and down-regulated of miRNAs for the assessment of gastric precancerous lesions, have also been proposed but not implemented routinely. Studies have evaluated the diagnostic and prognostic value of miRNAs in human gastric cancer with the method of meta-analysis or in systematic reviews[24].Several miRNAs, such as miR-21, miR-17-5p, etc, which have been proved to be potential biomarks for gastric cancers.With the method of meta-analysis, we evaluate the diagnostic and prognostic value of miR-92a in gastric cancer at present study.The results of the study showed that different assay type, type of the sample and sample size did not have a significant effect on the overall diaganostic accuracy. Besides, more moderate specificity and sensitivity in the diagnosis of gastic cancer have been found.And we expand the number of articles for diagnostic value compared with Wei H et al and Liu H et al's studies[24, 25]. In the pronostic value, patiens who are with high expression of miR-92a have more longer OS compared with low expression.On a par with Ren C et al's study[26], which only included two studies that investigated the prognostic value of miR-92a in gastric cancer, the present study included more articles, thus could greatly enhance the reliability of the results.

The significant role of miR-92a has been found in several cancers, one study indicated that overexpression of miR-92a is associated with osteosarcoma, colorectal cancer, non-small cell lung cancer or hepatocellular carcinoma[27].However, in gastric cancer, few schloars still have definite statements on the specific role of miR-92a desperately. Liu H [24]et al's study combined multi-miRNAs showed that the expression of miR-92a was increased inthe serum sample of gastric cancer. Patients with high miR-92a expression have a short survival time[27].But in opposite, one study[28] indicated that levels of miR-92a may be not related to gastric cancer, which found that contrasting results.Recently, Hideyuki Ohzawa et al [29] and Soeda N[30] et al's studies provide a new method for the prediction of gastric cancer, which regard the exosome miR-92a as a biomraker for the diagnosis tool of gastric cancer.And they revealed the same results that gastric cancer patients with

high expression of miR-92a and shorter overall survival time. Collectively, these conflicting results indicate the need for further studies on the role of miR-92a.

The diagmostic value of miR-92a has been demenstrated in several studies. With a sensitivity and specificity of 76% and 75%, Peng Q et al[31]found that vary expression between the patients with colorectal cancer and healthy controls.Moreover, their experiment indicated that the miR-92a-related combination markers achieved a higher level of diagnostic power.miR-92a also presented high accuracy of diagnosis for cervical cancer, with the sensitivity and specificity were 70% and 80%, respectively[32].For gastric cancer, the diagnostic accuracy of miR-92a varied significantly,with a sensitivity ranging from 39.3–97.5% and a specificity ranging from 70.8–97.8%.In addition, there are differences among these studies, such as assay type for qT-PCR, type of the sample and sample size.We found that miR-92a's high accuray of diganosis regardless of these differences.The results indicates that miR-92a can be used as a diagnostic indicator for gastric cancer.

For prognostic value of miR-92a, we founded that high expression of miR-92a may not be associated with poor clinical outcomes of gastric cancer patients, which was 1.46-fold higher risk for poor OS in both univariate and multivariate studies.However, untill we have finished extracting the articles, we have not found any the data of DFS(Disease free survival) and PFS(Progression-free survival) for miR-92a in gastric cancer. Currently, non-invasive biomarkers are more and more popular for assessing survival prognosis at any time before or after treatment.In our study, we have not obvious prognostic effect on gastric cancer, which is inconsistent with previous results of some previous prognostic studies, while our study may is the first one to report there is a negative association between high expression of miR-92a and patient survival.However, our sample size are larger than previous meta-analysis.In order to clarify the reults, more researches with sufficient data need to be done in the future.

Limitations

This study also has several limitations.(1) The sample size was still relatively small, in-cluding only 12 studies.Therefore, more well-designed studies for diagnostic and prognostic value of miR-92a are needed to obtain more reliable results.(2) The different ethnicities varied in the patients with gastric cancer. For example, the diagnostic meta-analysis and the prognostic meta-analysis only focused on Asians. Therefore, more researchers should pay attention to the impact of racial factors in the subsequent studies.(3) We only included articles published in English and Chinese, but did not cover articles in other languages.(4) some risk factors for the development and progression of gastric cancer need to be considered,such as Helicobacter pylori infection, unhealthy diet and etc, which will influence the reliablity of the study.(5) We only included articles published in English and Chinese, but did not cover articles in other languages.(6) The detection of miR-92a is based on qT-PCR, which having used the different type of assays that will affect the results of the study. Future studies should address these limitations to accurately validate the diagnostic and prognostic value of miR-92a in gastric cancer.

Conclusion

To sum up, we demenstrated for the first time that miR- 92a is promising to be a novel indicator for diagnosis of gastric cancer.But for the prognostic value of miR-92a, it may be not a significant biomarker for gastric cancer. Together, these findings pro-vide important evidence for further development of future non-invasive methods for diagnosing gastric cancer.

Abbreviations

AUC
Area under the ROC curve; DFS:Disease free survival; DOR:Diagnostic
odds ratio; FN
False negative; FP:False positive; HR:Hazard ratio;
miRNAs

MicroRNAs; NLR:Negative likelihood ratio; NOS:Newcastle-Ottawa
Scale; OS
Overall survival; PLR:Positive likelihood ratio; QUADAS-2:Quality assessment of diagnostic accuracy studies; TN:True negative; TP:True positive

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and matrials

Not applicable.

Authors' contribution

GHX and WYH proposed the conjecture and design of this study. GHX and LYT conducted the collection of materials and data management. Analysis andinterpretation of the data were performed by WYH and LYT. The writing andrevision of the manuscript were done by GHX. All authors havechecked the full text carefully and approved the final draft.

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Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable.

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Not applicable.

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Figures

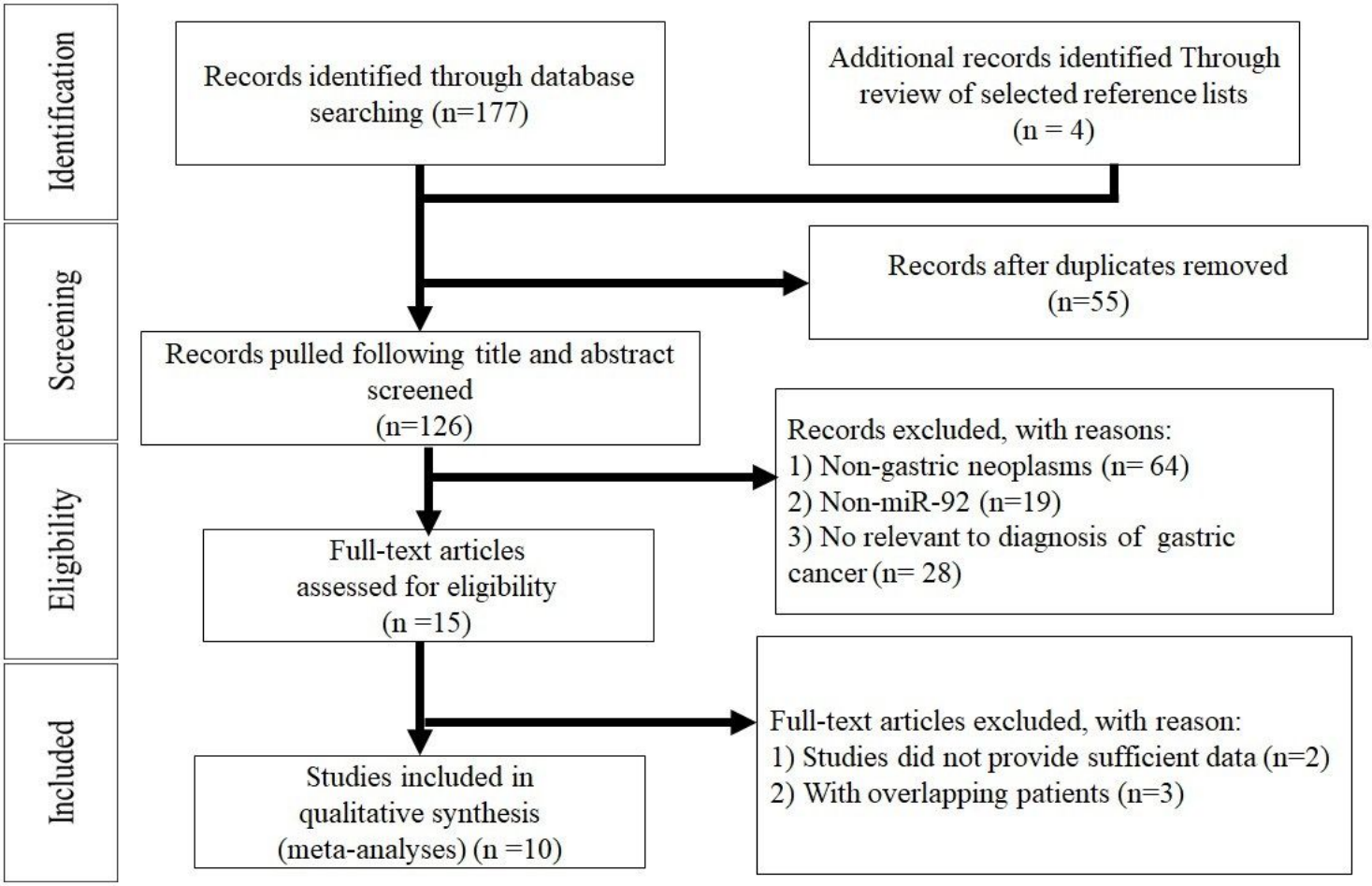

Figure 1

Flow chart of study selection

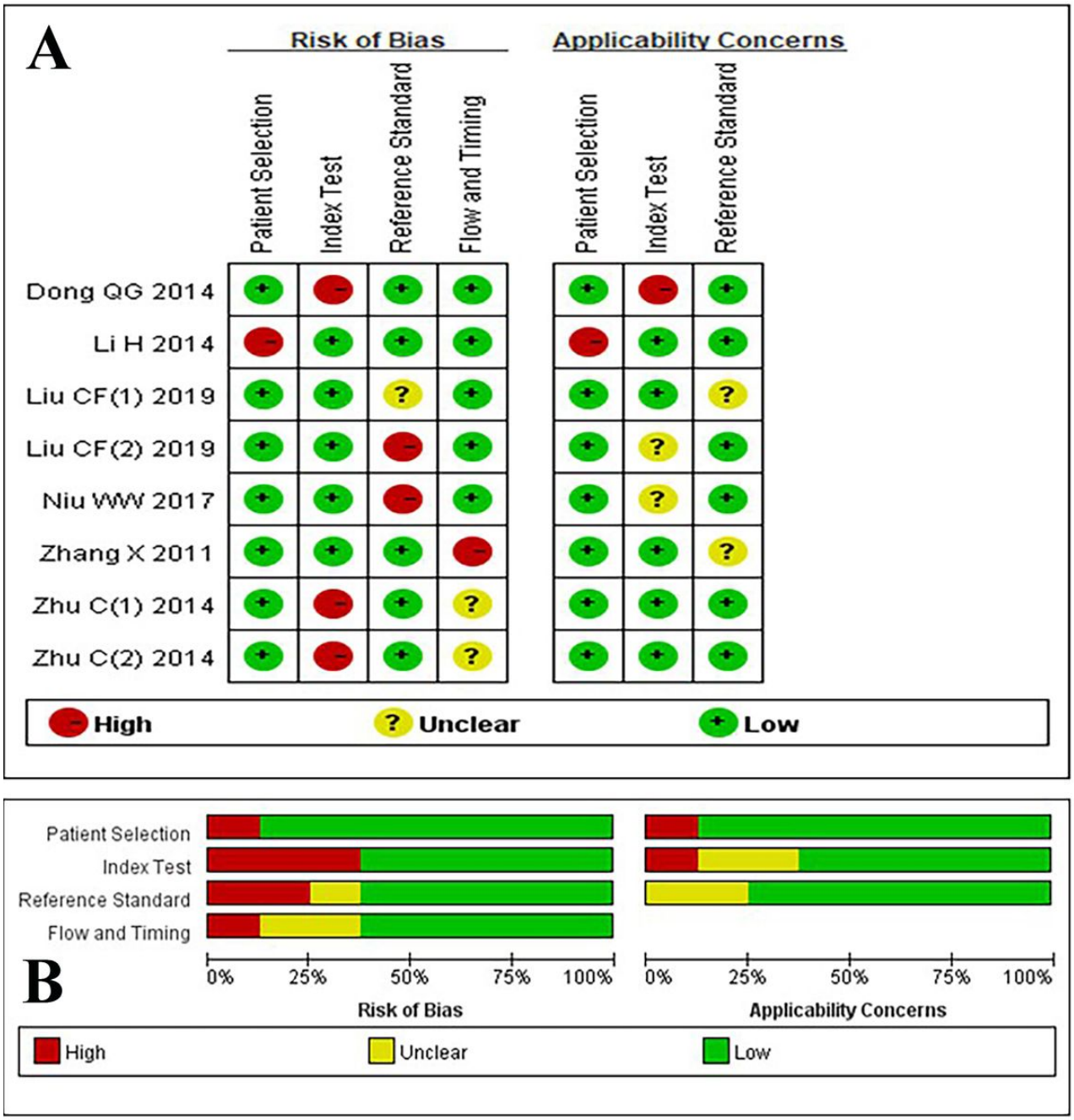

Figure 2

QUADAS-2 quality assessment. Investigators' assessment regarding each domain for included studies: (a) The graph and (b) summary

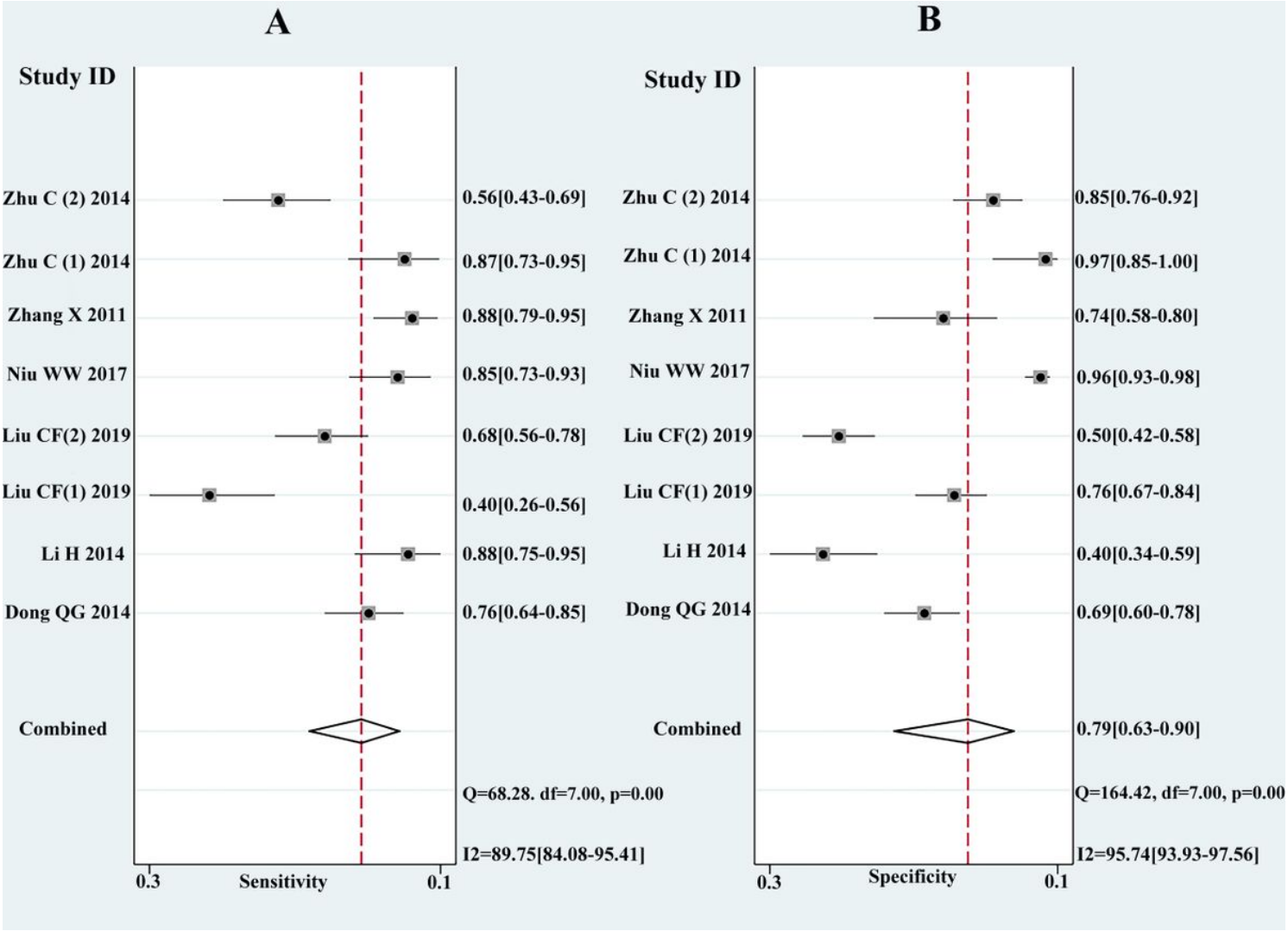

Figure 3

Forest plots of sensitivity (a), specificity (b) for miR-92a in the diagnosis of gastric cancer

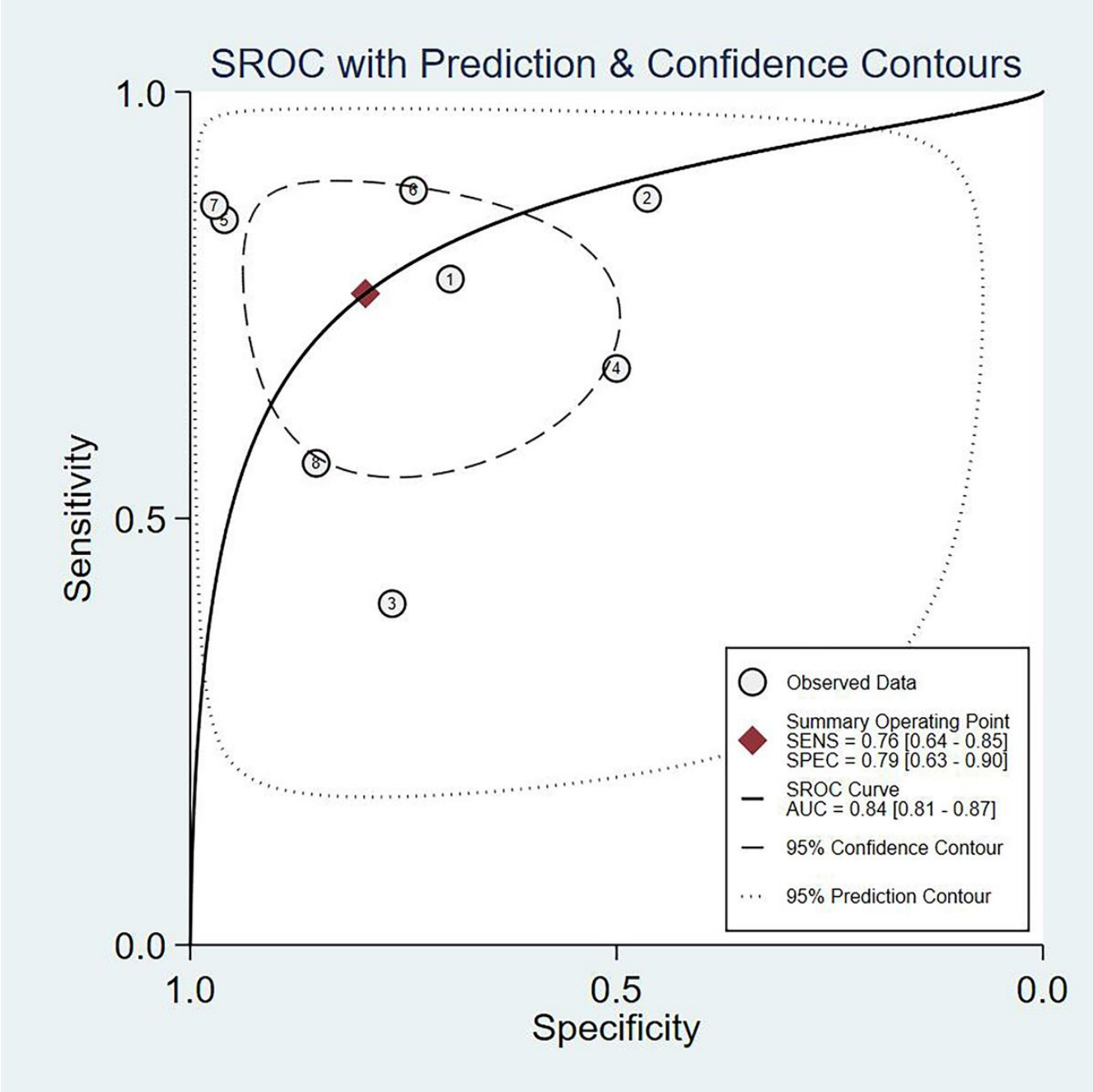

Figure 4

SROC curve plotted graph for the diagnostic value of miR-92a in gastric cancer.

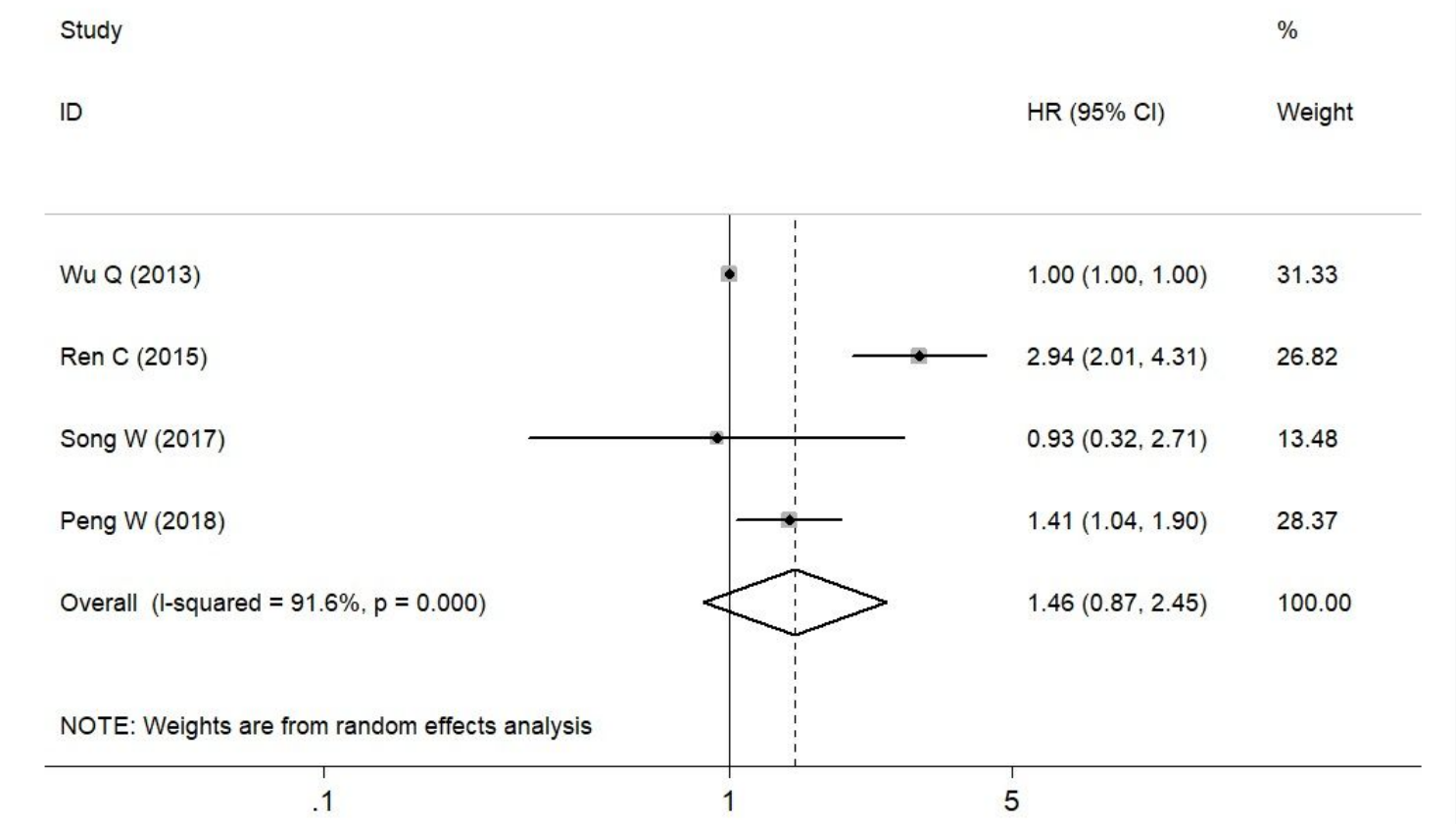

Figure 5

Forest plots of the studies that evaluated the hazard ratios of high miR-92a expression on univariate study

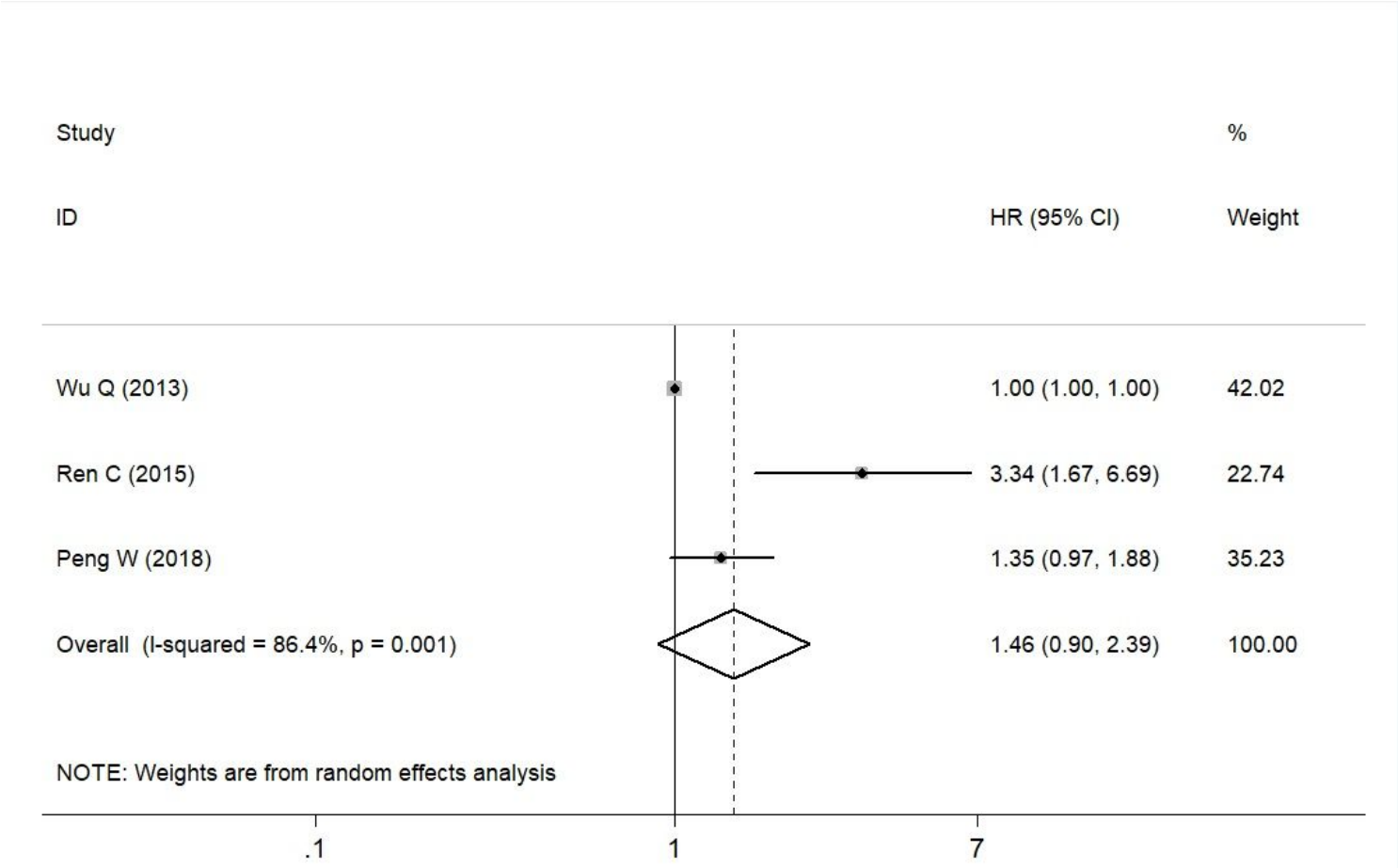

Figure 6

Forest plots of the studies that evaluated the hazard ratios of high miR-155 expression on multivariate study