The value of miR-155 as a biomarker for the diagnosis and prognosis of lung cancer: a systematic review with meta-analysis

Chuchu Shao
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Fengming Yang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Zhiqiang Qin
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Xinming Jing
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Yongqian Shu (shuyongqian1998@163.com)
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
https://orcid.org/0000-0003-3122-7139
Hua Shen
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

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Abstract

Abstract Background: In recent years, several studies have investigated the impact of miR-155 on the diagnosis and prognosis of LCa, but results of these researches were still controversial due to insufficient sample size. Thus, we carried out this systematic review and meta-analysis to figure out whether miR-155 could be a screening tool in the detection and prognosis of LCa. Methods: A meta-analysis of 13 articles with 19 studies was performed by retrieving the PubMed, Embase and other bibliographic databases. We screened all correlated literaters until December 1st, 2018. For the diagnostic value of miR-155 in LCa, SEN, SPE, PLR, NLR, DOR and AUC were pooled to evaluate the accuracy of miRNA-155 in the diagnosis of LCa. Subgroup and meta-regression analyses were performed to distinguish the potential sources of heterogeneity between studies. For the prognositic value of miR-155 in LCa, the pooled HRs and 95% CIs of miRNA-155 for OS and DFS/ PFS were calculated. Results: For the diagnosis analysis of miR-155 in LCa, the pooled SEN and SPE were 0.82 (95% CI: 0.72-0.88) and 0.78 (95% CI: 0.71-0.84), respectively. Besides, the pooled PLR was 3.75 (95% CI: 2.76-5.10), NLR was 0.23 (95% CI: 0.15-0.37), DOR was 15.99 (95% CI: 8.11-31.52) and AUC was 0.87 (95% CI: 0.84-0.90), indicating a significant value of miR-155 in the LCa detection. For the prognostic analysis of miR-155 in LCa, up-regulated miRNA-155 expression was not significantly associated with a poor OS (pooled HR = 1.26, 95% CI: 0.66-2.40) or DFS/PFS (pooled HR = 1.28, 95% CI: 0.82-1.97). Conclusions: This meta-analysis demonstrated that miR-155 could be used as a potential biomarker in the diagnosis of LCa but not an effective biomarker for predicting the prognosis of LCa. Furthermore, more well-designed researches with larger cohorts were warranted to confirm the value of miR-155 for the diagnosis and prognosis of LCa. Keywords: lung cancer, miR-155, diagnosis, prognosis, biomarker

Background

Lung cancer (LCa), as the dominant cause of cancer-associated deaths all over the world, remains a serious global public health issue to human beings [1]. Due to lack of effective early screening tools and therapeutic techniques, the clinical outcome of LCa patients remains very poor [2]. Thus, a growing number of reserches are commited to finding useful non-invasive biomarkers for cancer detection or predict outcomes, specially in the early stages [3, 4]. However, not all biomarkers have appropirate sensitivity and specificity at the same time like AFP (alpha-fetoprotein), which has been widely applied in hepatocellular carcinoma detection clinically and monitoring development and prognosis of the disease at any time. Therefore, it is urgent to identify a novel comprehensive biomarker that can be used to screen in the early stage of LCa or predict clinical outcomes in advance to provide guidance for cancer therapy.

A great number of studies have shown that microRNAs (miRNAs) could be used as emerging potential biomarkers for cancer diagnosis, predicting clinical outcomes and monitoring disease conditions. MiRNAs are a class of short, high conserved noncoding RNAs which can modulate the target gene expression in a post-transcriptional manner [5]. Increasing evidences revealed that miRNAs participate in diverse biological processess including cellular multiplication, apoptosis, differentiation, invasion, metastasis, etc [6]. Moreover, miRNAs are easy to isolate from human body fluids (serum, plasma, etc)

combined with excellent stability and non-invasive advantages [7]. Hence, miRNAs might be promising biomarkers in the cancer for early diagnosis, prognosis or clinical treatment responses prediction.

Notably, miR-155 has been widely studied as an oncogene involved in multiple cancers, including colorectal cancer, gastric cancer, breast cancer, non-small cell lung cancer and so on [8-12]. Recently, several studies showed that aberrant expression of miR-155 was tied to the diagnosis and prognosis of the patients with LCa. However, due to different sample sizes, ethnicities and detection methods, these articles showed conflicting results [13]. Hence, this comprehensive meta-analysis was conducted based on previous studies to further elaborate the diagnostic and prognostic value of miR-155 for LCa.

Methods

Search strategy

The systematic literature search was performed based on PubMed, Embase and other databases for eligible original literatures until December 1st, 2018. The relevant keywords included the following items: “miR-155” or “microRNA-155” or “miRNA-155”, and “lung cancer” or “NSCLC” or “lung”, and “prognosis” or “diagnosis” or “detection” or “variants”. The MeSH terminology and relevant keywords were randomly combined in order to ensure acquiring the most comprehensive data. 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, the following criteria were adopted: (1) Research focus on patients with definite diagnosis of LCa; (2) Detection of miR-155 expression in plasma, serum or other human body fluids; (3) Sufficient data of assessing the coorelation between miR-155 over-expression and poor overall survival (OS), disease free survival (DFS) and progression-free survival (PFS) in LCa patients; (4) Available data of true positive (TP), false positive (FP), false negative (FN), true negative (TN) or clear sample size combined with sensitivity (SEN) and specificity (SPE) to calculate the area under the ROC curve (AUC) for diagnostic analysis. In addition, the studies would be excluded according to the following criteria: (1) Non case-control studies, letters, reviews, comments; (2) Non-English or Chinese studies; (3) No data available for LCa diagnosis and prognosis; (4) Duplicates or the same samples used in previous publications.

Data extraction

All Data were extracted from the included studies by two investigators (SCC and YFM), the uncertain results were reviewed by the third investigator (QZQ). The extracted data consist of following items: first author's name, country, year of publication, ethnicity of the population studied; number of patients and controls; assay type; and diagnostic results of SEN, SPE, TP, FP, FN, and TN; or prognostic outcomes including HRs of elevated miR-155 expression for OS/DFS/PFS. In addition, if not directly available from

each article, data was extracted from the Kaplan-Meier curve using the previously described method to infer HR with 95% CI.

Quality assessment

Two researchers (SCC and YFM) in our institution assessed whether each included literature met the quality standards separately. Then, another researcher (QZQ) will reevaluate and make a unified conclusion if there is a discrepancy between first two researchers. For diagnostic meta-analysis, the quality assessment was conducted following the guidelines of the the Quality assessment of diagnostic accuracy studies 2 (QUADAS-2) [14]. This tool consists of 4 domains for assessing the risk and applicability of bias. The four areas (patient selection, index test, reference standard, and flow and timing) are refined into 14 specific questions. Each item has a rating of "Yes", "No" or "Unclear", corresponding to the scores of -1, 1 and 0, respectively (Figure 2). For prognostic meta-analysis, the quality of each included article was assessed by the Newcastle-Ottawa Scale (NOS), which is one of the most authoritative tools for assessing the quality of non-randomized studies [15, 16]. By scoring one by one, the total quality score ranges from 0 to 9. Studies with a final score > 6 were considered high-quality.

Statistical analysis

For diagnostic accuracy studies, the SEN, SPE, PLR, NLR and corresponding 95% CI from included studies were pooled to initially assess the diagnostic value of circulating miR-155 in LCa. The summary receiver operating characteristic (SROC) curve was then drawn based on the original data, and the area under the SROC curve (AUC) was calculated to comprehensively determine the diagnostic accuracy of miR-155, taking into account the trade-off between SEN and SPE. To assess the heterogeneity across studies, the X^2-based Q-statistic and I^2 statistic were utilized. The I^2 square value typically fluctuates within a range of 0 (unobserved heterogeneity) to 100% (maximum heterogeneity). P value <0.05 or I^2>50% was recognized statistically significant [17]. If the studies were proved to be homogenous, a fixed-effect model would be utilized for further analysis. If not, the random-effect model would be utilized [18]. Subsequently, subgroup and meta-regression analyses were carried out to find the potential sources of heterogeneity. Finally, the publication bias of all the included diagnostic accuracy studies was assessed by Deeks' funnel plots (significant at $P < 0.05$) [19].

For prognostic meta-analyses, a combination of the pooled HR and 95% CI was calculated to elucidate the link between high expression of miR-155 and cooresponding OS/DFS/PFS of LCa patients. Cochran's Q test and I^2 statistics were applied to evaluate the heterogeneity of the pooled results [20]. In addition, Begg's and Egger's tests were selected to evaluate the potential publication bias. All above statistical analysis was performed by the statistical software STATA (version 12.0) [21].

Results

Literature search results

Based on a systematic search on the above databases, 363 records related to miR-155 in lung cancer were initially identified. Then, 245 duplicates were deleted following the inclusion and exclusion criteria described previously. 87 articles were subsequently excluded after reading the titles and abstracts. As a result, the remaining 31 articles were all downloaded to obtain valid information individually. After sceening the full texts carefully, 12 studies were elimated due to lack of available diagnostic or prognostic related data. Ultimately, this meta-analysis included 13 articles covering 19 cohort studies [22-34]. Among them, 6 articles with 8 cohorts focused on the miR-155 expression for LCa diagnostic accuracy, whereas 7 articles including 11 studies related to the prognostic value of miR-155 in LCa **(Figure 1).**

Studies characteristics and quality assessment

In the 8 eligible studies for diagnosis, a total of 457 cases and 342 controls were included. The main characteristics of these enrolled studies were presented in **Table 1**. Among these 8 studies, three ethnic groups were analyzed, in which six from Asians, one from Africans, and the remaining from Caucasians. All included studies detected expression of miR-155 through qRT-PCR using SYBR or Tagman reagent. The results of the QUADAS-2 quality evaluation were shown in **Figure 2A&2B**. Most studies were consistent with the criteria in QUADAS-2, indicating that the enrolled studies are suitable for quantitative synthesis.

In the 7 included articles for prognosis, a total of 1382 participants were identified for assessing OS/DFS/PFS, respectively. The characteristics of the qualified studies were summarized in **Table 2**. The population of these studies were classified into Asians and Caucasians from five different countries, including China, France, America, Japan and Norway. In addtion, the detailed quality assessment for each study scored following the guidlines of NOS is shown in **Table 3**.

Diagnosis meta-analysis

Pooled diagnostic value of miR-155 in LCa

The forest plots results were presented in **Figure 3A&3B** as follows: the pooled SEN and SPE were 82% (95% CI: 78-88%) and 78% (95% CI: 71-84%). The PLR and NLR were 3.75 (95% CI: 2.76-5.10) and 0.23 (95% CI: 0.15-0.37) respectively (**Figure 3C&3D**). Meanwhile, the pooled DOR was 15.99 (95% CI: 8.11-31.52) (**Figure 5A**) and the area under SROC (AUC) was 0.85 (95% CI: 0.82-0.88) (**Figure 6A**). All above data demonstrated the relatively high diagnostic value of miR-155 in LCa.

Subgroup analysis

To distinguish the potential origins of heterogeneity between studies, a subgroup analysis was perfomed based on Assay type. The pooled results of this subgroup analysis were shown in **Figure 4**. It can be observed that studies based on SYBR qPCR method showed similar results: the SEN was 86% (95% CI: 77-91%), SPE was 79% (95% CI: 71-86%), PLR was 4.11 (95% CI: 2.99-5.65) and NLR was 0.18 (95% CI: 0.12-0.28), respectively. The summary DOR was 22.69 (95% CI: 13.90-37.04) (**Figure 5B**) and AUC was 0.89 (95% CI: 0.86-0.91) (**Figure 6B**).

Prognosis meta-analysis

The main outcome of the prognostic meta-analysis was to evaluate the correlation between miR-155 expression and OS/DFS/PFS of LCa patients. In the 4 studies evaluating OS, the pooled HR and its 95% CIs were calculated using a random-effect model with a result of 1.26 (95% CI: 0.66-2.40) (**Figure 7A**). Meanwhile, for 7 studies evaluating DFS/PFS , the combined HR with 95% CIs was 1.28 (95% CI: 0.82-1.97) (**Figure 7B**). To sum up, the results given above proved that there was not significant correction between over-expression of miRNA-155 and poor OS or DFS/PFS.

Publication bias and meta-regression analyses

The potential publication bias across the enrolled diagnostic studies was accessed by the Deeks' funnel plot test whereas the prognostic studies evaluated using Begg's funnel plot and Egger's test. The Deeks' funnel plot was symmetry and reached a P value of 0.951 above 0.05, indicating there is no obvious publication bias in these included studies. The P values of Begg's tests for OS and DFS/PFS were 0.497 and 0.453. The results of Egger's test(OS: P = 0.785, DFS/PFS: P = 0.264, respectively) also proved no existence of publication bias. These results indicated that the data were reliable in the current meta-analysis.

Discussion

As a malignant tumor with extremely high mortality, LCa has gaining great attention and extensive researches during recent decades. With the development of surgical techniques, concurrent radiotherapy and chemotherapy, and imaging examination technology have greatly improved the prognosis of LCa patients. However, the most effective way to improve the survival of patients with LCa lies in early diagnosis and targeted treatment. Therefore, a large amount of researchers are committed to finding suitable non-invasive biomarkers to predict the diagnosis or prognosis of LCa, and provide directions for clinical treatment of LCa.

As vital regulators of various biological processes in cancer, miRNAs were regarded as perfect non-invasive biomarkers for human cancers [35-37]. MiR-155 has been widely reported to participate in the development and progression of diverse cancers, including lung cancer [37]. Several studies have demonstrated that up-regulated miR-155 is associated with the pathogenesis of LCa, suggesting that miR-155 acts as an oncogene in LCa [38, 39]. Zang et al revealed that miR-155 is involved in the development and progression of lung cancer. In their experiments, miR-155 was shown to modulate celluar poptosis and DNA damage via Apaf-1 mediated pathways to enhance the sensitivity of LCa cells to cisplatin [40]. Moreover, another study conducted by Katrien et al demonstrated that miR-155 induces increased resistance to chemotherapy in lung cancer cells by forming a feedback loop with TP53 [41]. In particular, they also found that over-expression of miR-155 combined with low expression of TP53 is significantly linked to poor OS of LCa patients. Based on that, miR-155 might be a novel ideal biomarker for LCa. In addition to the above studies focused on the molecular mechanism of miR-155 regulation in lung cancer cells, a number of cohort studies have investigated the coorelationship between miR-155

expression in different individuals with the diagnosis or prognosis of LCa to determine whether miR-155 as an ideal biomarker. [42, 43]. However, these results have not been corroborated and even contradictory. Thus, this meta-analysis appears to be necessary to figure out the diagnostic or prognostic value of miR-155 in LCa.

In the diagnosis meta-analysis, the total DOR and 95% CI of miR-155 was 15.99 (95% CI: 8.11-31.52). In addition, AUC and corresponding 95% CI were 0.85 (95% CI: 0.82-0.88), indicating that miR-155 could be a moderate diagnostic marker in the detection of LCa compared to healthy individuals. Subgroup analysis of Assay type revealed that studies based on SYBR had a higher DOR of 22.69 (95% CI: 13.90-37.04) and the higher AUC of 0.89 (95% CI: 0.86-0.91), which might be the possible sources of heterogeneity. Therefore, miR-155 might be an applicable biomarker for LCa detection. On the other hand, the prognostic meta-analysis suggested that up-regulated levels of miR-155 might not be associated with poor clinical outcomes of LCa patients, which was 1.26-fold higher risk for poor OS and 1.28-fold higher risk for poor DFS/PFS. These results might caused by different genetic backgrounds, environmental exposures and detection methods. Recently, accumulating studies worldwide have shown that expression levels of miRNAs in different individuals have significant predictive value in cancers . Currently, the detection of miRNAs in tissue samples has been applied to current tumor prognosis studies, but the detection of serum/plasma samples and other human body fluids appears to be more portable, non-invasive, and can effectively assess survival prognosis at any time before or after treatment. It can even play a role in the patient's life-long disease surveillance and is of great help to clinical thearapy. This meta-study found that miR-155 has no obvious prognostic effect on LCa, which is inconsistent with the results of some previous prognostic meta-analyses. But the amount of samples included in this study is larger than previous mata-analysis, more researches with sufficient data will be needed to verify this result.

Ultimately, several limitations still existed in this meta-analysis as follows: (1) Racial factors were not comprehensive enough, and the population is too monotonous. For example, the diagnostic meta-analysis is mainly for Asians and Africans while the prognostic meta-analysis only focused on Caucasians and Asians. Therefore, more researchers should pay attention to the impact of racial factors in the subsequent studies. (2) Unpublished studies may contain negative results, but we are not available include them, which potentially lead to lack of credibility in the data. (3) We only included articles published in English and Chinese, but did not cover articles in other languages. (4) The sample size was still relatively small, including only 19 studies, which may undermine the reliability of our findings. Therefore, more well-designed studies based on larger samples and sufficient data are required to verify the diagnostic and prognostic value of circulating miR-155 in LCa.

Conclusions

To summarize, our meta-analysis demonstrated for the first time that circulating miR-155 is promising to be a novel biomarker for diagnosis of LCa. However, miR-155 is not an effective biomarker for predicting the prognosis of LCa. Together, these findings provide important evidence for further development of future non-invasive methods for diagnosing LCa. Further large-scale relevant studies with better designs

and more comprehensive data support will help to clarify the diagnostic and prognostic value of miR-155 in LCa.

Abbreviations

AUC: Area under the ROC curve

DFS: Disease free survival

DOR: Diagnostic odds ratio

FP: False positive

FN: False negative

HR: Hazard ratio

LCa: Lung cancer

miRNAs: MicroRNAs

NLR: Negative likelihood ratio

NOS: Newcastle-Ottawa Scale

OS: Overall survival

PFS: Progression-free survival

PLR: Positive likelihood ratio

QUADAS: Quality assessment of diagnostic accuracy studies

TN: True negative

TP: True positive

Declarations

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

SYQ and SH proposed the conjecture and design of this study. SCC and YFM conducted the collection of materials and data management. Analysis and interpretation of the data were performed by QZQ and YFM. The writing and revision of the manuscript were done by SCC and JXM. All authors have checked the full text carefully and approved the final draft.

Authors' information

Chuchu Shao: s_chuchu@sina.com

Fengming Yang: yfmdoctor@163.com

Zhiqiang Qing: qinzq_urology@sina.com

Xinming Jing: 13615135110@163.com

Hua Shen: medshenhua@163.com

Yongqian Shu:shuyongqian1998@163.com;

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Tables

Table 1. Characteristics and methodology assessment of 8 studies included in the diagnosis meta-analysis

First author	Year	Country	Ethnicity	Case/Control	Assay type	SEN (%)	SPE(%)	TP	FP	FN	TN
Qing Geng (1) [21]	2014	China	Asian	25/25	SYBR	87.00	87.00	22	3	3	22
Qing Geng (2) [21]	2014	China	Asian	126/60	SYBR	86.00	84.00	108	10	18	50
Feng Gao [19]	2013	China	Asian	36/32	SYBR	72.20	68.70	26	8	10	22
Dongfang Tang (1) [20]	2013	China	Asian	62/60	TaqMan	59.70	75.00	37	15	25	45
Dongfang Tang (2) [20]	2013	China	Asian	34/32	TaqMan	67.60	65.60	23	11	11	21
Amal A. [22]	2013	Egypt	African	65/37	SYBR	95.40	62.20	62	14	3	23
Carina Roth [23]	2011	Germany	Caucasian	35/28	TaqMan	87.70	88.90	31	3	4	25
Dali Zheng [24]	2011	China	Asian	74/68	SYBR	80.36	83.93	59	11	15	57

Table 2. The main features of 11 included studies in prognostic meta-analysis

First author	Year	Country	Ethnicity	Case	Outcome	HR (95%CIs)	P value
Xinying Xue (1) [31]	2016	China	Asian	80	OS	0.52 (0.24-1.14)	0.045
Xinying Xue (2) [31]	2016	China	Asian	80	DFS	0.83 (0.30-2.31)	0.054
Yi Gao [27]	2014	China	Asian	162	OS	2.31 (1.48-3.61)	<0.001
Johannes Voortman [28]	2010	France	Caucasian	637	OS	0.91 (0.72–1.13)	0.390
Mitch Raponi [25]	2009	America	Caucasian	54	OS	2.30 (1.00-5.60)	0.060
Ce´ line Sanfiorenzo [30]	2013	France	Caucasian	52	DFS	0.94 (0.15-5.74)	0.008
Motonobu Saito (1) [26]	2011	Japan	Caucasian	89	PFS	2.37 (1.27–4.42)	0.006
Motonobu Saito (2) [26]	2011	Japan	Caucasian	37	PFS	1.60 (0.73–3.52)	0.245
Motonobu Saito (3) [26]	2011	Japan	Asian	191	PFS	1.33 (0.77–2.29)	0.309
Tom Donnem (1) [29]	2011	Norway	Caucasian	191 (SCC)	PFS	0.45 (0.21-0.96)	0.039
Tom Donnem (2) [29]	2011	Norway	Caucasian	95 (AC)	PFS	1.87 (1.01-3.48)	0.047

OS: overall survival; DFS: disease free survival; PFS: progression-free survival;SCC:squamous cell carcinoma;AC:Adenocarcinoma

Table 3. Newcastle–Ottawa quality assessments scale

First author	Year	Quality indicators from Newcastle–Ottawa Scale								Scores
		1	2	3	4	5	6	7	8	
Raponi [25]	2009			–	–					7
Saito [26]	2011			–						8
Yi G [27]	2014			–	–					7
Voortman [28]	2010	–	–	–						6
Donnem [29]	2011		–	–	–					6
Sanfiorenzo [30]	2013			–						8
Xue [31]	2016			–					–	7

1. Representativeness of the exposed cohort; 2. Selection of the non-exposed cohort; 3. Ascertainment of exposure; 4. Outcome of interest not present at start of study; 5. Control for important factor or additional factor; 6. Assessment of outcome; 7. Follow-up long enough for outcomes to occur; 8. Adequacy of follow up of cohorts

Figures

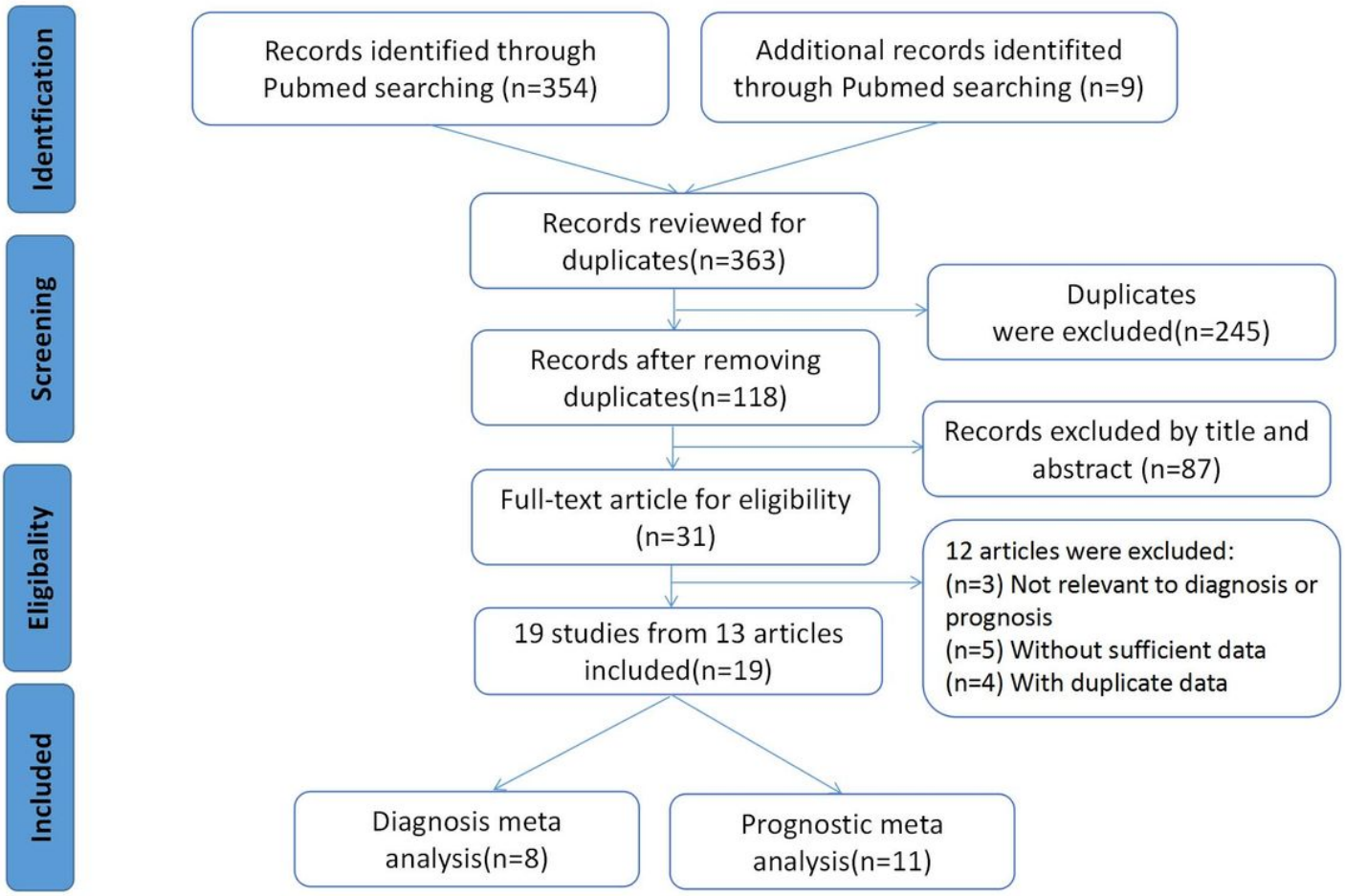

Figure 1

Flow chart of selection process.

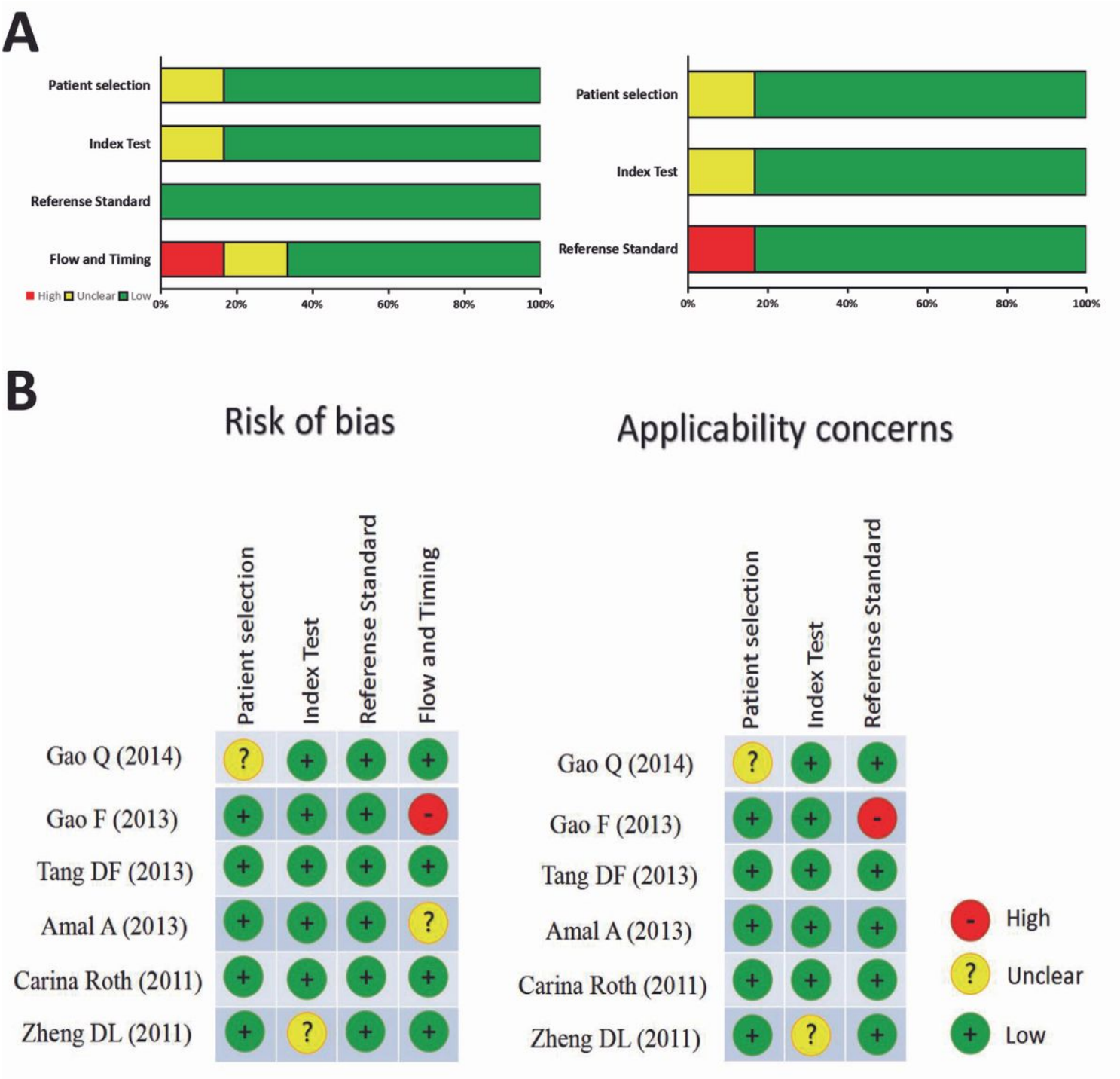

Figure 2

QUADAS-2 quality assessment. Investigators' assessment regarding each domain for included studies.

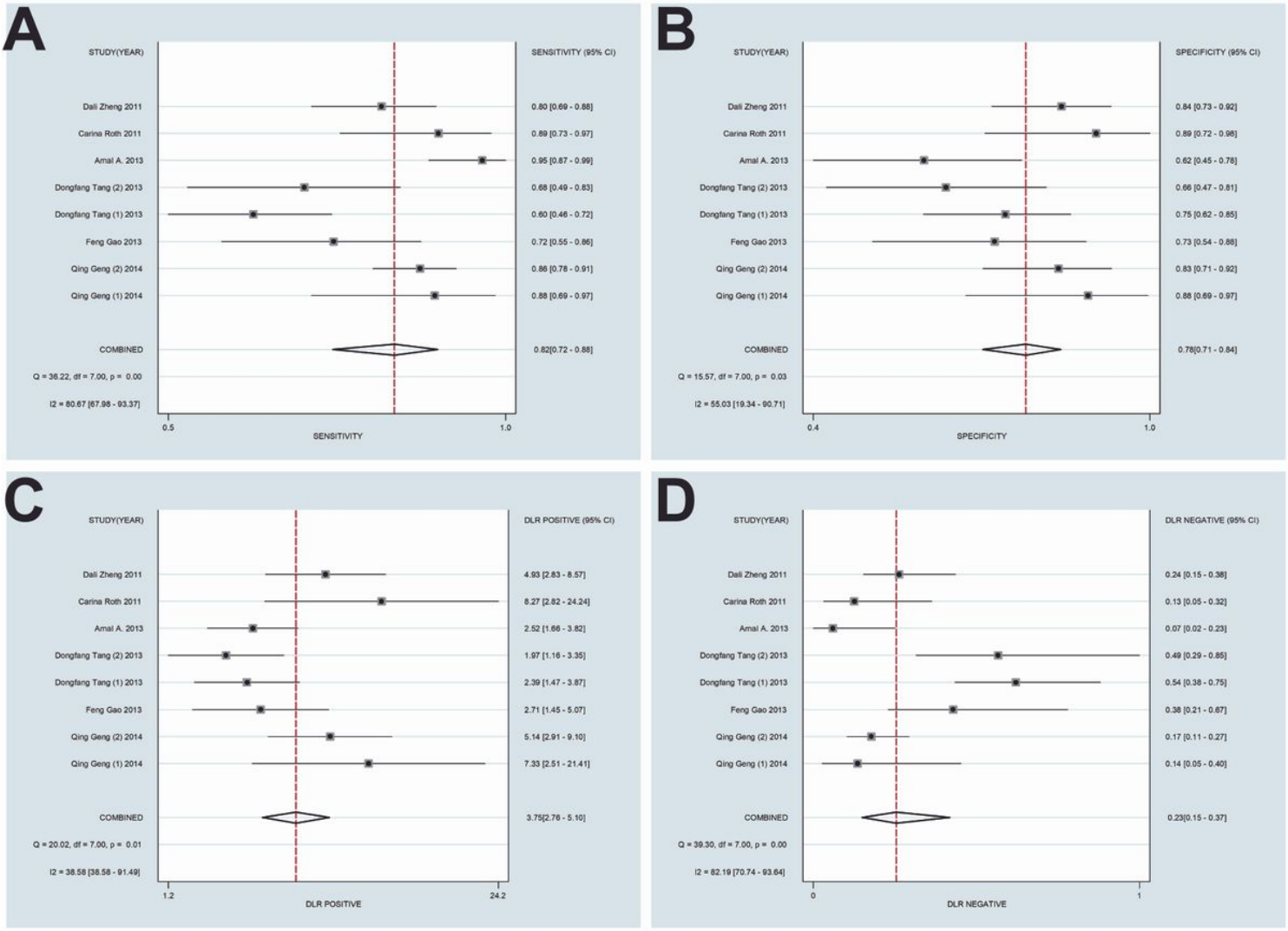

Figure 3

Forest plots of sensitivity (A), specificity (B), positive likelihood ratios (C) and negative likelihood ratios (D) for miR-155 in the diagnosis of LCa.

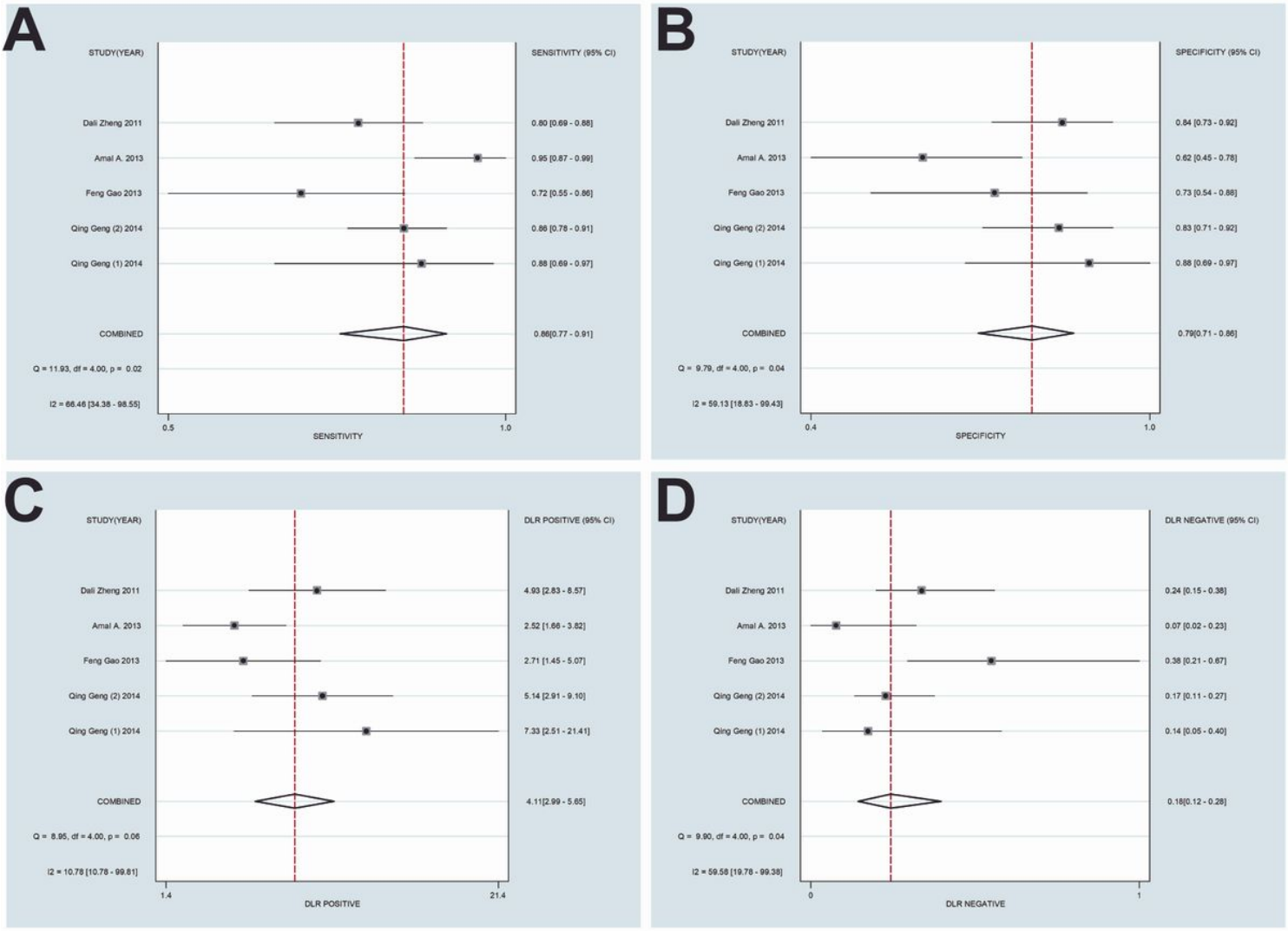

Figure 4

Subgroup analysis based on Assay type of sensitivity (A), specificity (B), positive likelihood ratios (C) and negative likelihood ratios (D) for miR-155 by SYBR in the diagnosis of LCa.

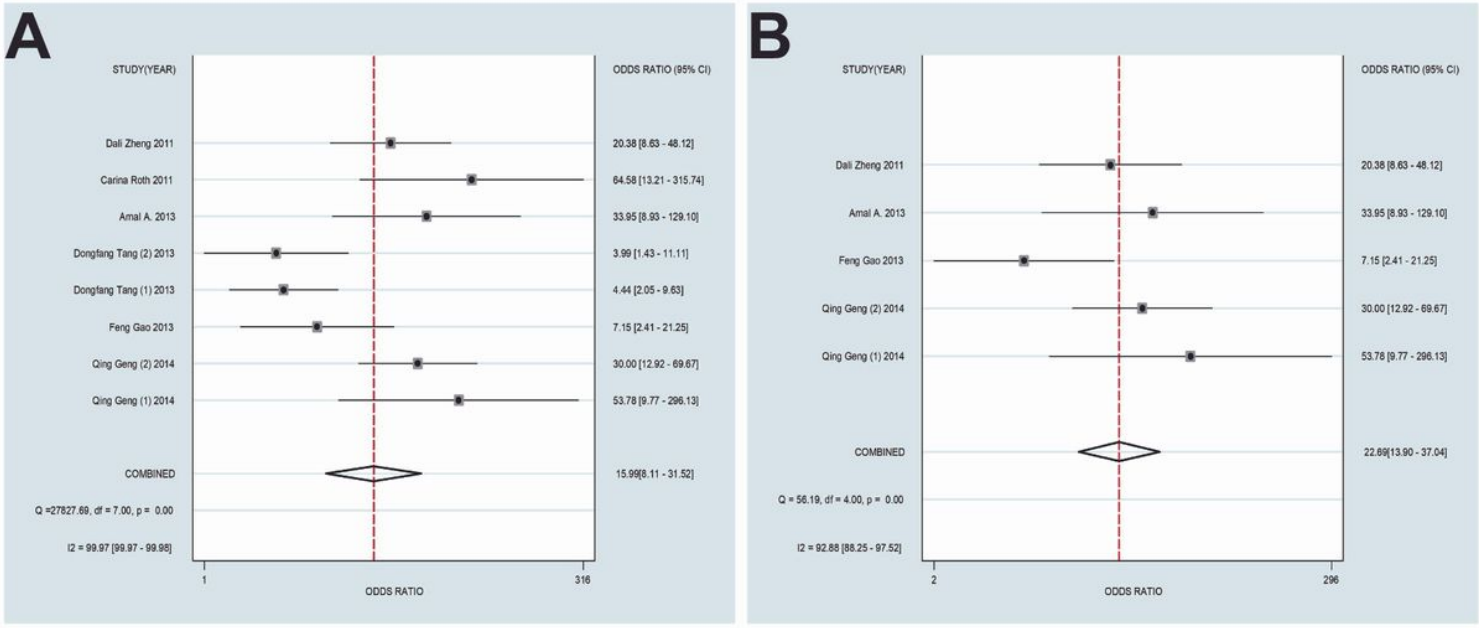

Figure 5

Forest plots of the diagnostic odds ratio (DOR) for miR-155 in the diagnosis of LCa. (A). All studies; (B). The studies based on SYBR.

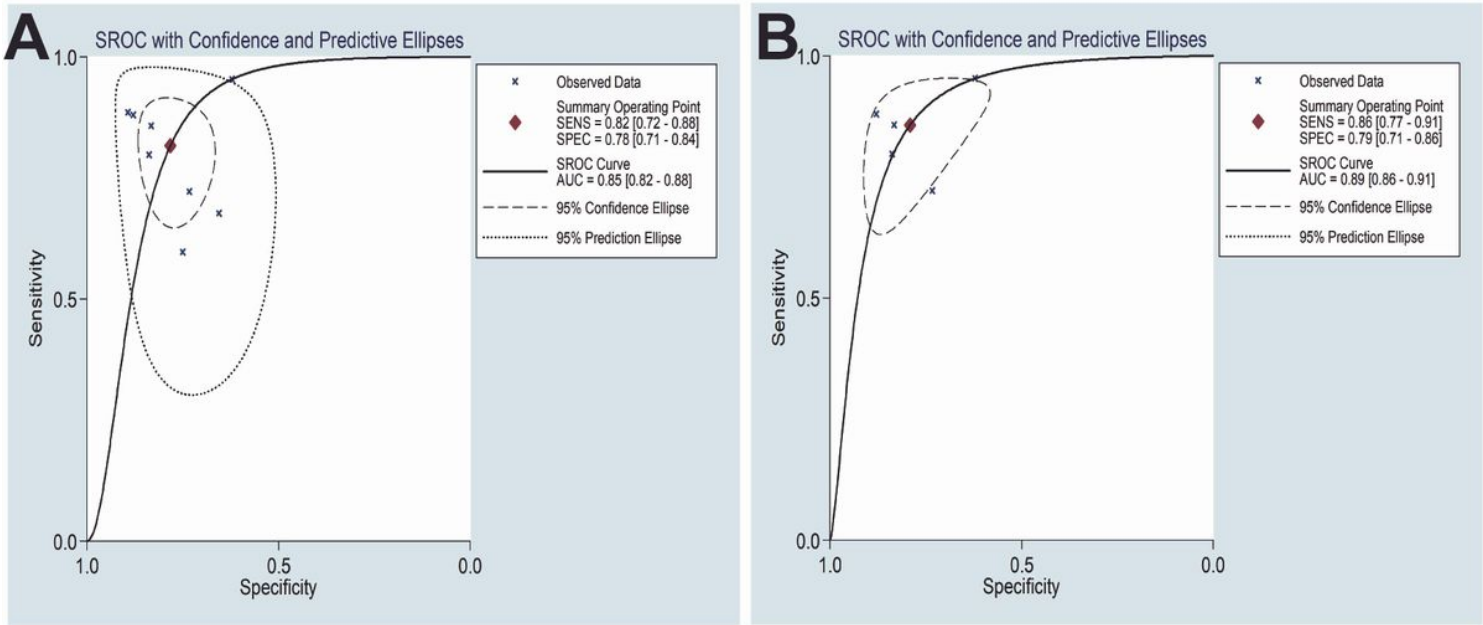

Figure 6

Summary receiver operating characteristic curves (sROC) from the hierarchical summary receiver operating characteristic model generated from the 8 studies that found that miR-155 was a diagnostic marker for LCa. (A). All studies; (B). The studies based on SYBR.

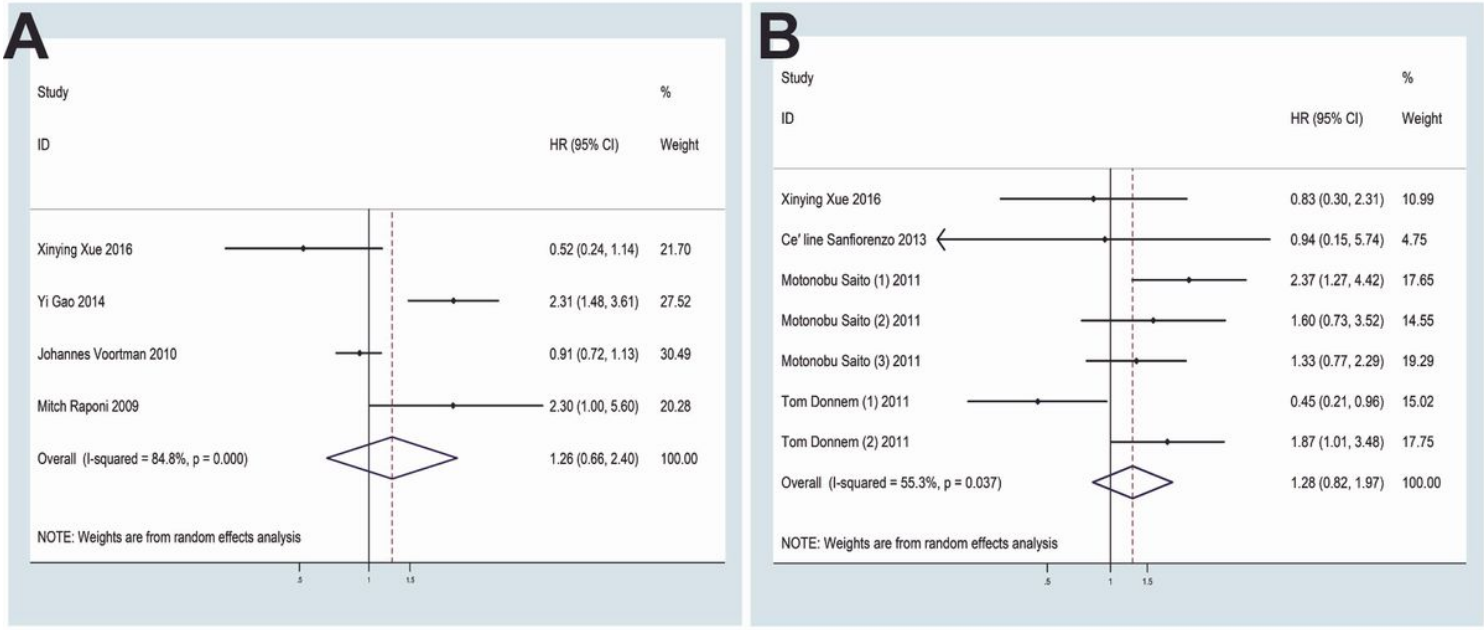

Figure 7

Forrest plots of the studies that evaluated the hazard ratios of high miR-155 expression.