ORIGINAL RESEARCH

MicroRNA-21 and microRNA-30c as diagnostic biomarkers for prostate cancer: a meta-analysis

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Background: Prostate cancer (PCa) is the second leading cause of cancer death in men. Several articles have reported that microRNA-21 (miR-21) and microRNA-30c (miR-30c) have diagnostic values for PCa, but the results are inconclusive. In order to precisely assess the diagnostic values of miR-21 and miR-30c for PCa, this meta-analysis is performed.

Methods: Articles were searched in the databases of PubMed, Embase, and Web of Knowledge (search date: September 6, 2018). Studies were included if they were designed to evaluate the diagnostic performance of miR-21 or miR-30c for PCa. Using Stata 12.0 and Meta-Disc 1.4, the pooled sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under curve (AUC) of the summary receiver-operating characteristic (SROC) curve with the corresponding 95% CI were calculated.

Results: Overall, ten studies (six studies for miR-21 and four for miR-30c) involving 1,371 participants were included in this meta-analysis. For miR-21, the pooled SEN and SPE were, respectively, 0.91 (95% CI: 0.87–0.94) and 0.88 (95% CI: 0.82–0.93), the pooled PLR and NLR were, respectively, 7.74 (95% CI: 4.81–12.47), 0.1 (95% CI: 0.06–0.15), the DOR was 77.64 (95% CI: 34.64–174.02), AUC of SROC was 0.95 (95% CI: 0.93–0.97). For miR-30c, the pooled SEN and SPE were, respectively, 0.74 (95% CI: 0.65–0.81) and 0.78 (95% CI: 0.72–0.83), the pooled PLR and NLR were, respectively, 3.39 (95% CI: 2.69–4.26), and 0.34 (95% CI: 0.26–0.44), the DOR was 10.06 (95% CI: 6.96–14.55), and AUC of SROC was 0.83 (95% CI: 0.79–0.86).

Conclusion : For PCa, miR-21 is a good diagnostic biomarker and miR-30c is a moderate diagnostic biomarker.

Keywords: microRNA-21, microRNA-30c, prostate cancer, meta-analysis

Introduction

As a complex disorder resulting from the combined effects of multiple environmental and genetic factors, prostate cancer (PCa) is the second leading cause of cancer death in men.[1] In Europe, it accounts for >92,300 deaths annually.[2] As a routine assay test in clinic, prostate-specific antigen (PSA) in serum is not specific for PCa, some evaluated PSA levels may induce false-positive due to infection or hyperplasia. Therefore, it is necessary to find novel effective biomarkers to diagnose PCa.

MicroRNAs, a family of small noncoding RNAs (19±22 nucleotides), are stable and easy to accurately measure. MicroRNAs are differentially expressed in normal tissues and cancers, contributing to cancer development and progression.[3] MicroRNA-21(miR-21), an anti-apoptotic agent functioning via p53 network, can target and inhibit tumor suppressor gene *PTEN* expression to promote PCa cell proliferation and

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invasion.[4,5] MicroRNA-30c (miR-30c) has been acknowledged as a tumor suppressor in various human cancers, such as ovarian cancer, gastric cancer, and PCa.[6]

With respect to diagnostic abilities of miR-21 and miR-30c for PCa, several studies have been conducted, but their results are inconclusive.[7–14] For example, Porzycki et al found specificity (SPE) of miR-21 to diagnose PCa was 0.75, while Yang et al found it could reach 0.93.[8,9] What's more, Huang found sensitivity (SEN) of miR-30c was 0.82, while Chen et al found it was only 0.6.[11,14] In order to precisely assess the diagnostic values of miR-21 and miR-30c for PCa, this meta-analysis is performed.

Methods

This meta-analysis was conducted according to the guidelines of the PRISMA statement (Table S1).[15]

Eligibility criteria

This meta-analysis selected the patients diagnosed as PCa and the control consisted of healthy people or patients with benign prostate disease. The index tests, which included miR-21 and miR-30c from serum, plasma, mononuclear cell, and tissue, were assessed by fluorescence quantitative PCR. Reference standard was histopathological test, PCa was diagnosed based on histopathological confirmation.

Studies were included if they met following inclusion criteria: 1) studies were designed to evaluate the diagnostic performance of miR-21 or miR-30c for PCa; 2) PCa was diagnosed based on histopathological confirmation and the control group consisted of healthy people or patients with benign prostate disease; 3) 2×2 contingency tables could be directly extracted or calculated; and 4) articles were written in English.

Search strategy

Articles published prior to September 6, 2018, were systematically searched in the databases of PubMed, Embase, and Web of Knowledge. Search terms were as follows: ("microRNA" or "miRNA" or "miR") and ("prostate cancer" or "prostate carcinoma") and ("diagnosis" or "sensitivity" or "specificity"). Search strategy is shown in Table S2. In addition, cited references from relevant articles were examined to select other relevant articles. Two reviewers independently searched the articles. Any disagreements between the two reviewers were resolved by discussion.

Study selection

The titles and abstracts of the identified articles were examined by two reviewers. Those articles falling under the exclusion criteria (reviews, case reports, letters, comments, conference abstracts, or meta-analyses; animal studies; duplicate studies) were not considered. The full texts were then rescreened and evaluated more thoroughly for eligibility using the same exclusion criteria. Disagreement between the two reviewers was discussed until a consensus was reached.

Data extraction

The following data were extracted or calculated from retrieved articles by the two reviewers: first author, year of publication, country of participants, specimen type, source of control group, sample size, microRNAs as control for normalization, microRNAs as biomarker, relative expressions in case group compared with control group, diagnostic SEN and SPE values, values of true positive (TP), false positive (FP), false negative (FN) and true negative (TN).

Methodological quality assessment

Two reviewers assessed the methodological quality of included studies according to the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool.[16] Patient selection, index test, reference standard, flow, and timing were used to evaluate the risk of bias and the first three domains were applied to assess applicability concerns.

Statistical analysis

Statistical analyses were undertaken utilizing Stata 12.0 (StataCorp, College Station, TX, USA) and Meta-Disc 1.4 (Cochrane Colloquium, Barcelona, Spain). Diagnostic threshold effects were inspected with the Spearman rank correlation analysis. Heterogeneity was measured using Cochrane-Q test and I^2 index. $P<0.05$ for Q test or $I^2 >50\%$ designated heterogeneity. The pooled SEN and SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic score (DS), diagnostic odds ratio (DOR), and area under curve (AUC) of the summary receiver operating characteristic (SROC) curve with the corresponding 95% CI were calculated using a bivariate binomial mixed model. Deeks' funnel plot asymmetry analysis was performed to identify publication bias. Sensitivity analysis was conducted to assess the stability.

Results

Literature search and study characteristics

A total of 420 records were identified through database searching. After removing duplicates, the titles and abstracts for 280 records were screened for eligibility. Of these, 46 records were identified and full-text articles were retrieved.

Thirty-eight manuscripts were excluded through assessment of the full-text articles and eight remaining articles encompassing ten studies were included in the meta-analysis (Figure 1).

The ten included studies owned 1,371 participants (737 PCa patients and 634 controls). Their characteristics and the numbers of TP, FP. FN, and TN with the corresponding SEN, SPE are listed in Table 1. The number of included studies for miR-21 and miR-30c were, respectively, six and four. Countries of participants for miR-21 involved Poland, China, and Egypt, while miR-30c only involved China. Relative expressions of miR-21 in case group were higher than that in control group. On the contrary, relative expressions of miR-30c were lower in case group. Two studies assessed miR-30c from PCa cancer tissue and PCa adjacent normal tissue,[7, 11] and other two studies assessed miR-30c from plasma of PCa patients and control group.[14] Studies assessed miR-21 from serum, plasma, mononuclear cell of PCa patients, and control group.

Methodological quality assessment

Quality assessment of included studies was conducted using the QUADAS-2 tool (Figures 2 and 3). The majority of included studies satisfied most domains of QUADAS-2. The unclear situation existed in the domains of patient selection and index test because there were variations in control group, specimen, and microRNAs as control for normalization.

Diagnostic values

For miR-21, the Spearman rank correlation coefficient was −0.841 (P=0.036), suggesting that there were no diagnostic threshold effects. The pooled SEN and SPE were, respectively, 0.91 (95% CI: 0.87–0.94) and 0.88 (95% CI: 0.82–0.93) (Figure 4). I^2 for SEN and SPE were, respectively, 0% (P=0.58) and 48.9% (P=0.08), showing no significant heterogeneity among studies. The pooled PLR and NLR were, respectively, 7.74 (95% CI: 4.81–12.47) and 0.1 (95% CI: 0.06–0.15) (Figure 5). The pooled DS and DOR were,
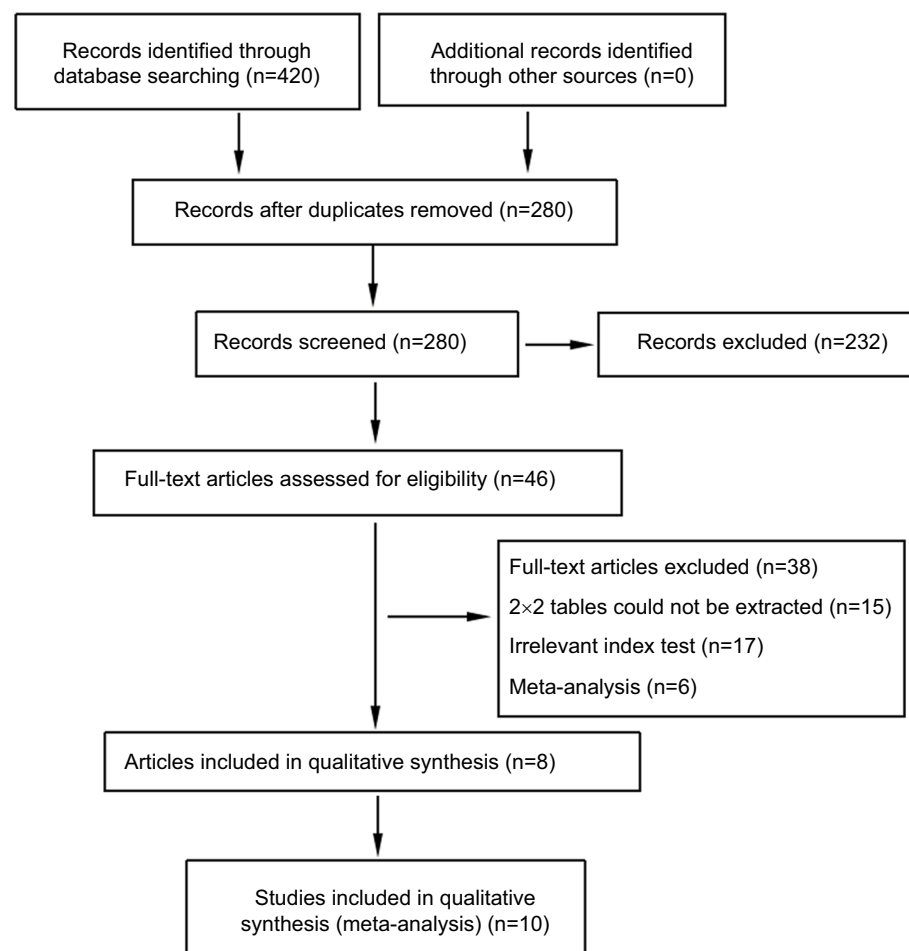

Figure 1 Flow diagram of study selection.

Table I Characteristics of included studies

Author	Year	Country	Specimen	Control group	MiR as control	Case size	Control size	MiR as biomarker	Relative expression[a]	SEN	SPE	TP	FP	FN	TN
Zhu et al[7]	2018	China	Tissue[b]		U6	187	187	miR-30c	Low	0.72	0.80	135	37	52	150
Porzycki et al[8]	2018	Poland	Serum	HP	U6	20	10	miR-21	High	0.90	0.75	18	2	2	8
Yang et al[9]	2016	China	Mononuclear cell	PBPD	miR-16	92	85	miR-21	High	0.94	0.93	86	6	6	79
Yang et al[9]	2016	China	Mononuclear cell	HP	miR-16	92	97	miR-21	High	0.95	0.93	87	7	5	90
Gao et al[10]	2016	China	Plasma	PBPD	U6	57	28	miR-21	High	0.88	0.75	50	7	7	21
Huang et al[11]	2016	China	Tissue[b]		U6	44	44	miR-30c	Low	0.82	0.80	36	9	8	35
Huang et al[12]	2015	China	Mononuclear cell	HP	U6	75	75	miR-21	High	0.88	0.86	66	11	9	64
Kotb et al[13]	2014	Egypt	Serum	PBPD	SNORD47	10	10	miR-21	High	0.90	0.90	9	1	1	9
Chen et al[14]	2012	China	Plasma	HP	U6	80	54	miR-30c	Low	0.79	0.69	64	17	16	37
Chen et al[14]	2012	China	Plasma	PBPD	U6	80	44	miR-30c	Low	0.61	0.83	49	8	31	36

Notes: [a], Relative expression of miR-21 or miR-30c as biomarker in case group compared with control group. [b], Include PCa cancer tissue and PCa adjacent normal tissue, cancer tissue was regarded as case group and adjacent normal tissue as control group.
Abbreviations: PBPD, patients with benign prostate disease; HP, healthy people; SEN, sensitivity; SPE, specificity; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

respectively, 4.35 (95% CI: 3.54–5.16) and 77.64 (95% CI: 34.64–174.02) (Figure 6). AUC of SROC curve was 0.95 (95% CI: 0.93–0.97) (Figure 7).

For miR-30c, the Spearman rank correlation coefficient was 0.80 (P=0.2), suggesting no existence of diagnostic threshold effects. The pooled SEN and SPE were, respectively, 0.74 (95% CI: 0.65–0.81) and 0.78 (95% CI: 0.72–0.83) (Figure 8). I^2 for SEN and SPE were, respectively, 67.69% (P=0.03) and 21.41% (P=0.28), revealing that significant heterogeneities existed among studies. The pooled PLR and NLR were, respectively, 3.39 (95% CI: 2.69–4.26) and 0.34 (95% CI: 0.26–0.44) (Figure 9). The pooled DS and DOR were, respectively, 2.31 (95% CI: 1.94–2.68) and 10.06 (95% CI: 6.96–14.55) (Figure 10). AUC of SROC curve was 0.83 (95% CI: 0.79–0.86) (Figure 7).

Publication bias

As shown in Deeks' funnel plots (Figure 11), publication biases were likely absent with symmetrical funnel shapes. The P-values for the funnel plot asymmetry tests (P=0.43 for miR-21 and P=0.95 for miR-30c) confirmed lack of publication biases.

Sensitivity analysis

Sensitivity analysis was performed by eliminating studies one by one. As shown in Table S3, the pooled SEN and corresponding heterogeneities of miR-21 and miR-30c were not dominantly influenced by removing any study.

Discussion

The pooled SEN and SPE of miR-21 were, respectively, 0.91 and 0.88, and the AUC of SROC was 0.95, presenting a good diagnostic ability of miR-21. The pooled PLR of 7.74 indicated that PCa probability increased by 7.74-fold with positive miR-21 result. Conversely, the pooled NLR of 0.1 showed the probability could only be 10% when miR-21 result was negative. As a combination of PLR and NLR, DOR is a meaningful diagnostic index. With a DOR value of 77.64, it was confirmed that miR-21 could be a good diagnostic biomarker for PCa. Sensitivity analysis showed that the conclusion of this meta-analysis was robust. There is a research which suggests that miR-21 and androgen receptor axis can exert oncogenic effects in prostate tumors by downregulating transforming growth factor beta receptor II.[17]

For miR-30c, this meta-analysis showed that pooled SEN and SPE were, respectively, 0.74 and 0.78; furthermore AUC of SROC was 0.83, presenting a moderate diagnostic ability of miR-30c. Significant heterogeneities were found among
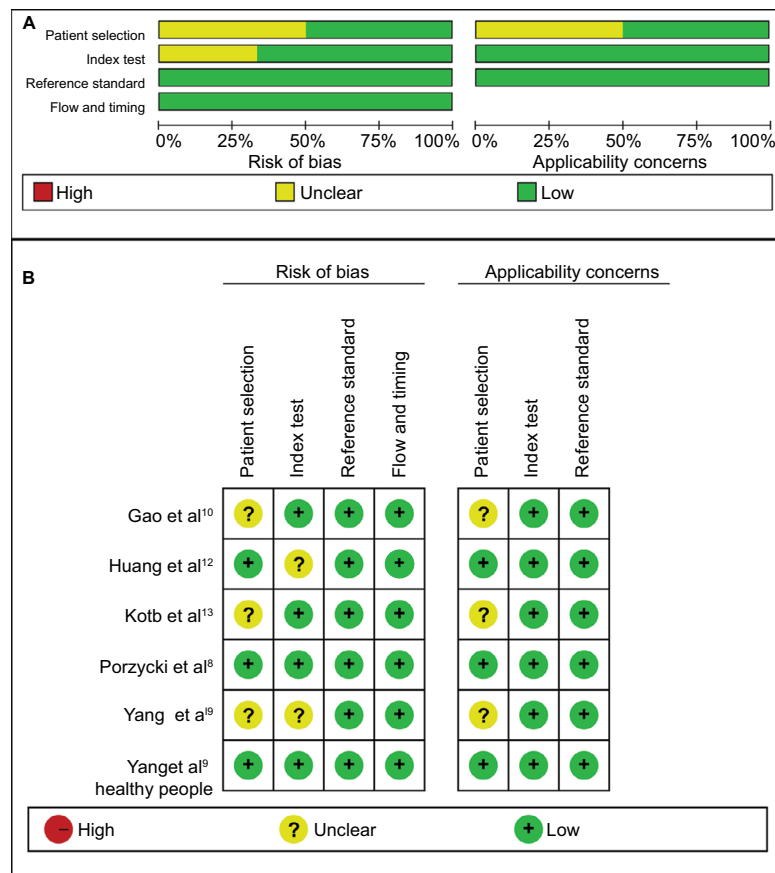
Figure 2 Quality assessment of miR-21 according to QUADAS-2 guidelines.
Note: (**A**) Risk of bias, (**B**) applicability concerns.
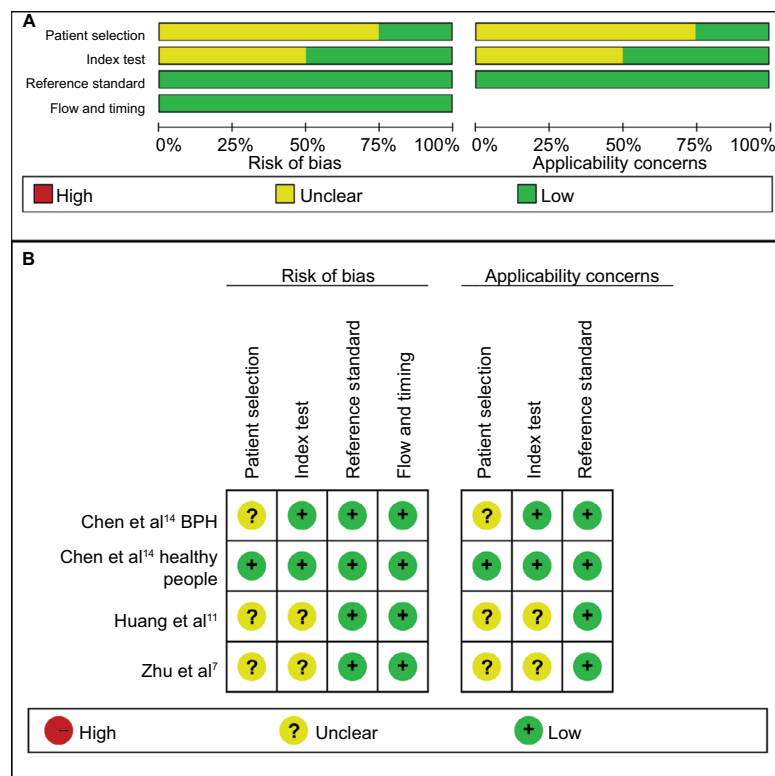

Figure 3 Quality assessment of miR-30c according to QUADAS-2 guidelines.
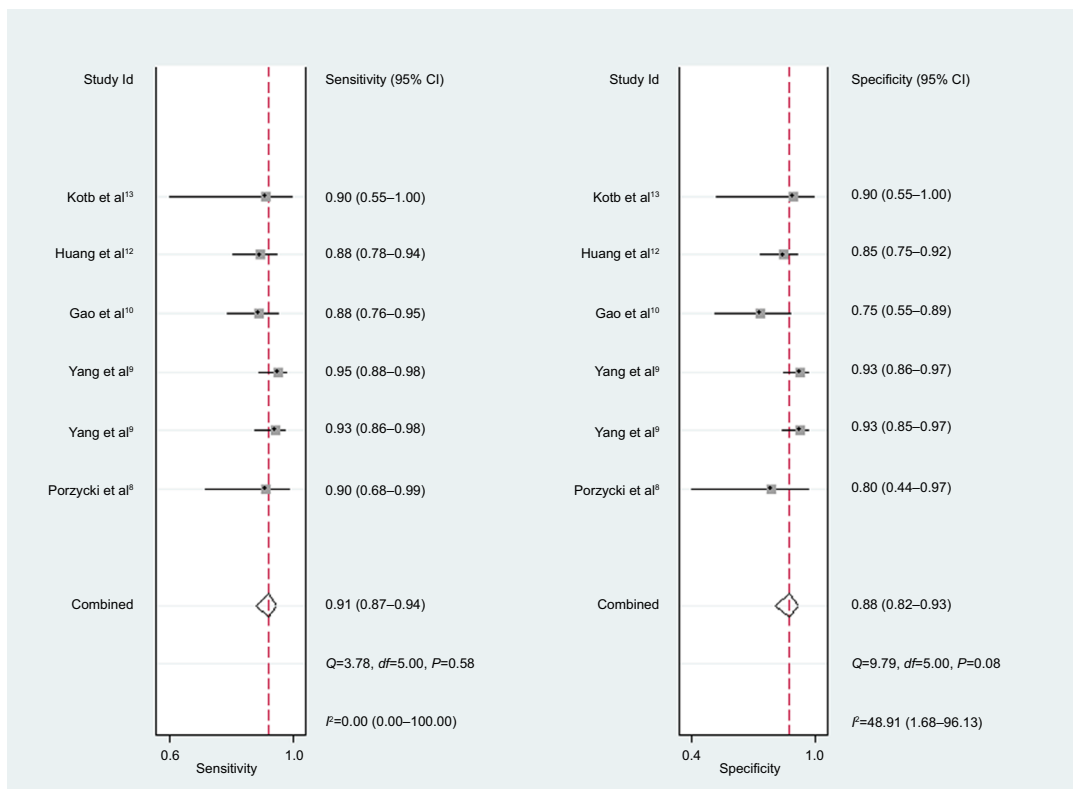**Note:** (**A**) Risk of bias, (**B**) applicability concerns.

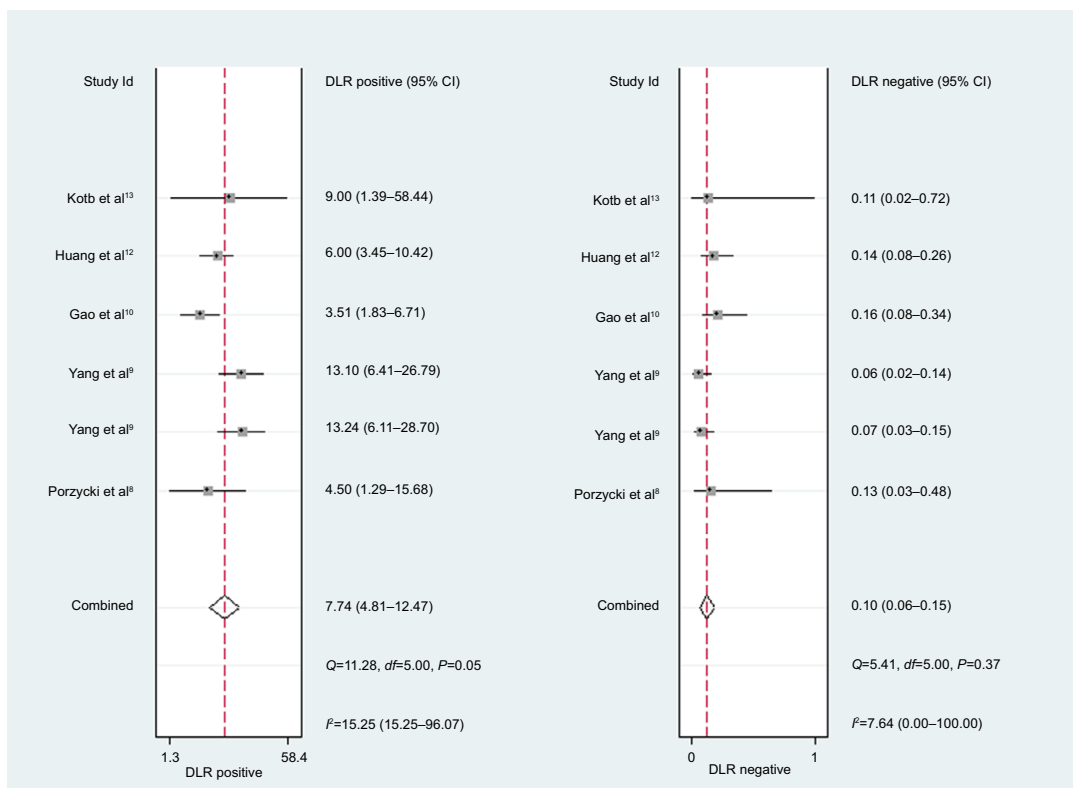**Figure 4** Forest plots of sensitivity and specificity for miR-21.

Figure 5 Forest plots of positive likelihood ratio and negative likelihood ratio for miR-21.
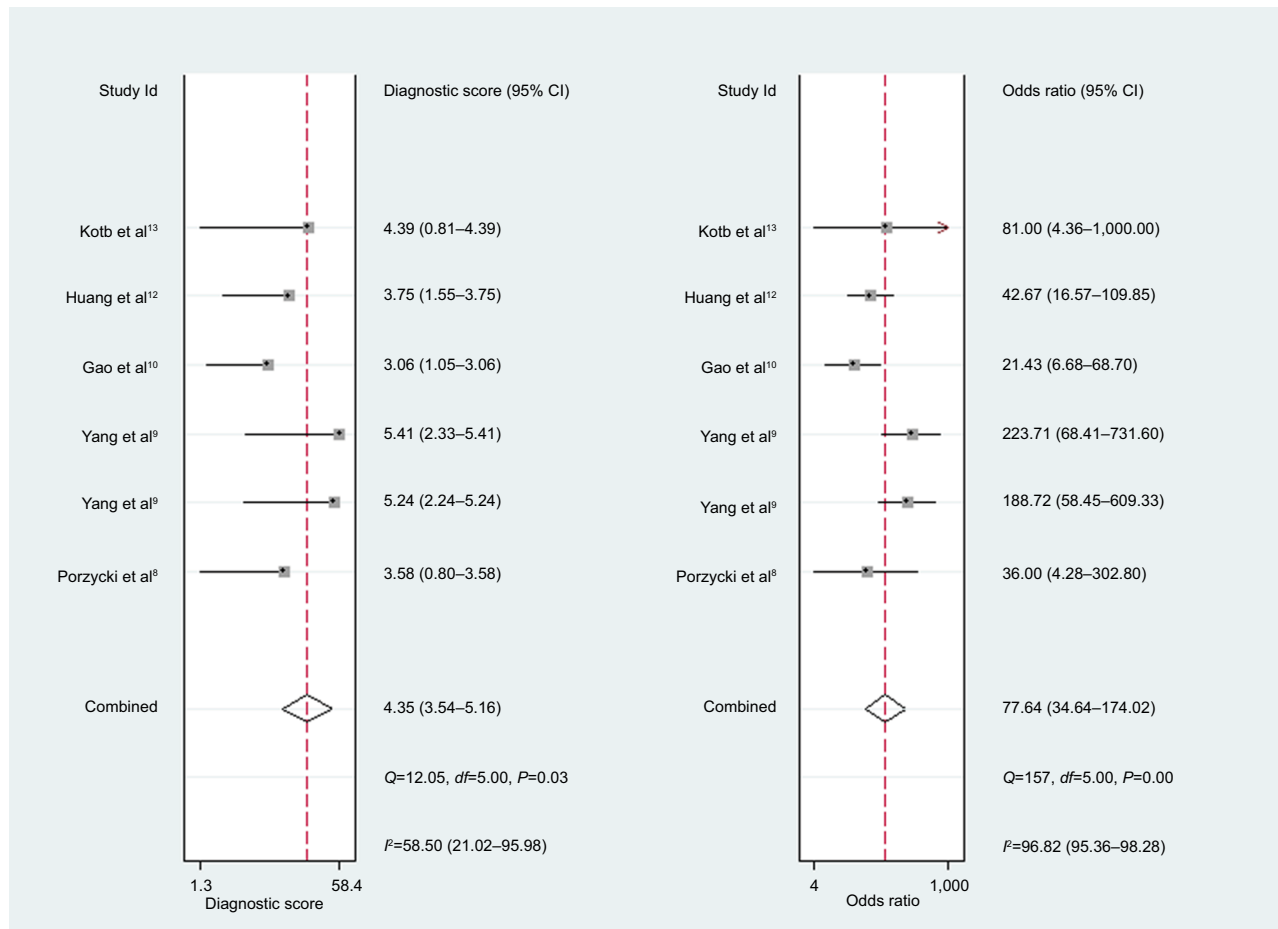**Abbreviation:** DLR, diagnostic likelihood ratio.

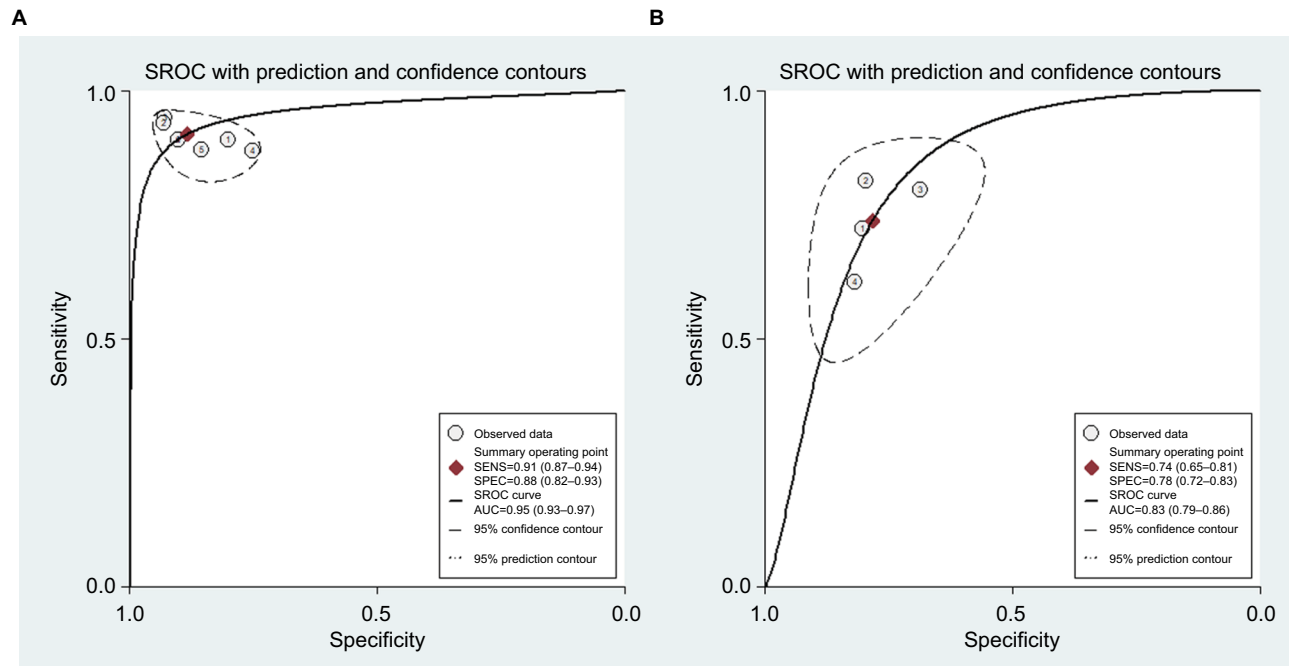**Figure 6** Forest plots of diagnostic score and diagnostic odds ratio for miR-21.

Figure 7 Summary receiver operating characteristic curves.
Note: (**A**) miR-21, (**B**) miR-30c.
Abbreviations: AUC, area under curve; SROC, summary receiver- operating characteristic; SENS, sensitivity; SPEC, specificity.
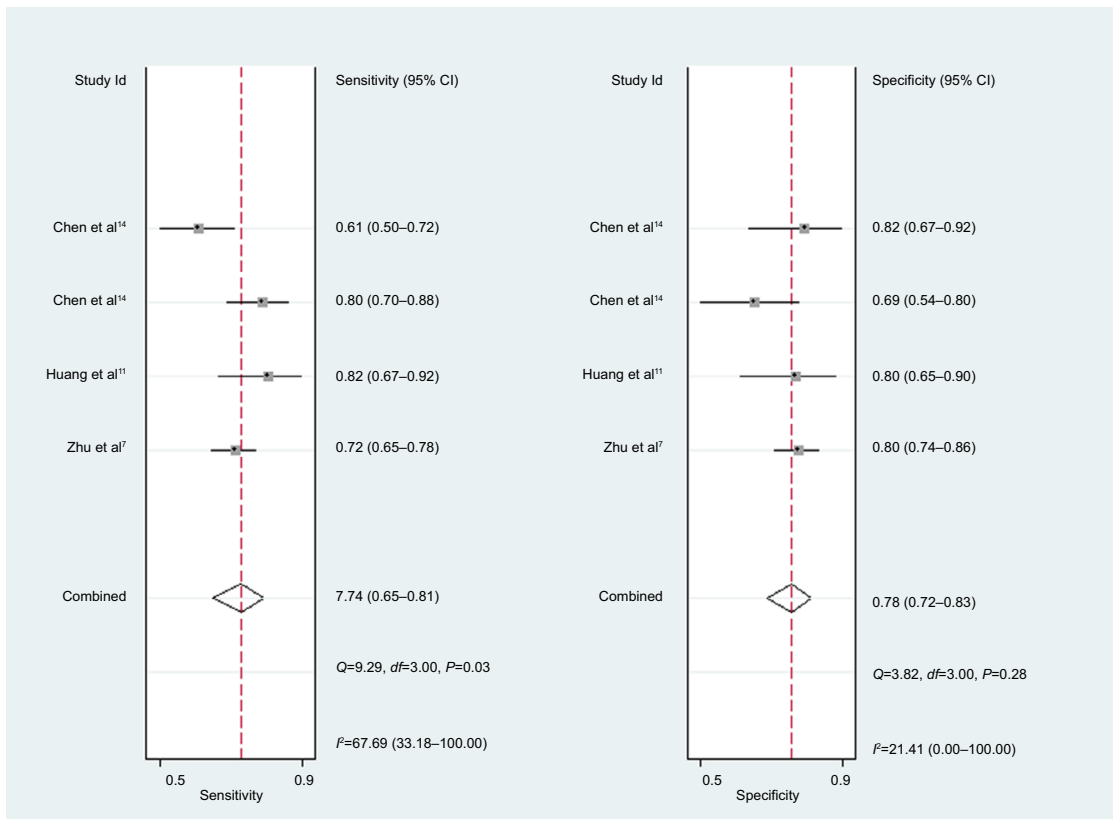
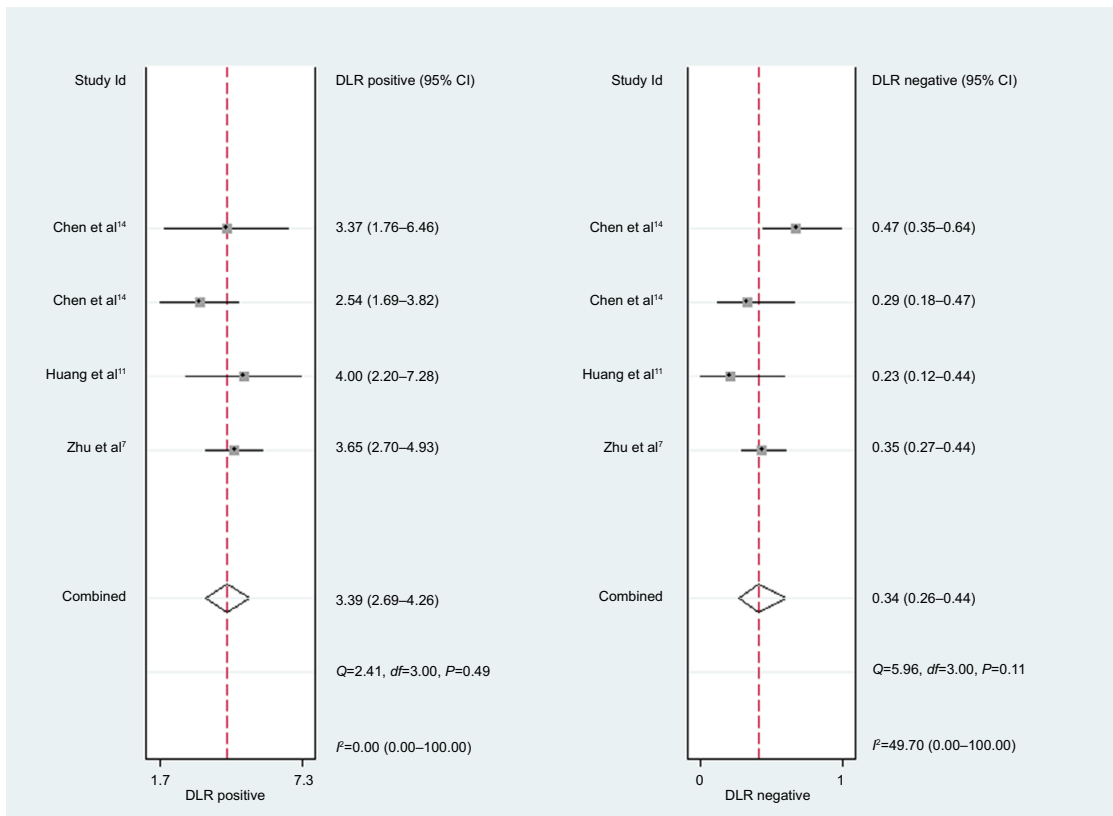**Figure 8** Forest plots of sensitivity and specificity for miR-30c.

Figure 9 Forest plots of positive likelihood ratio and negative likelihood ratio for miR-30c.
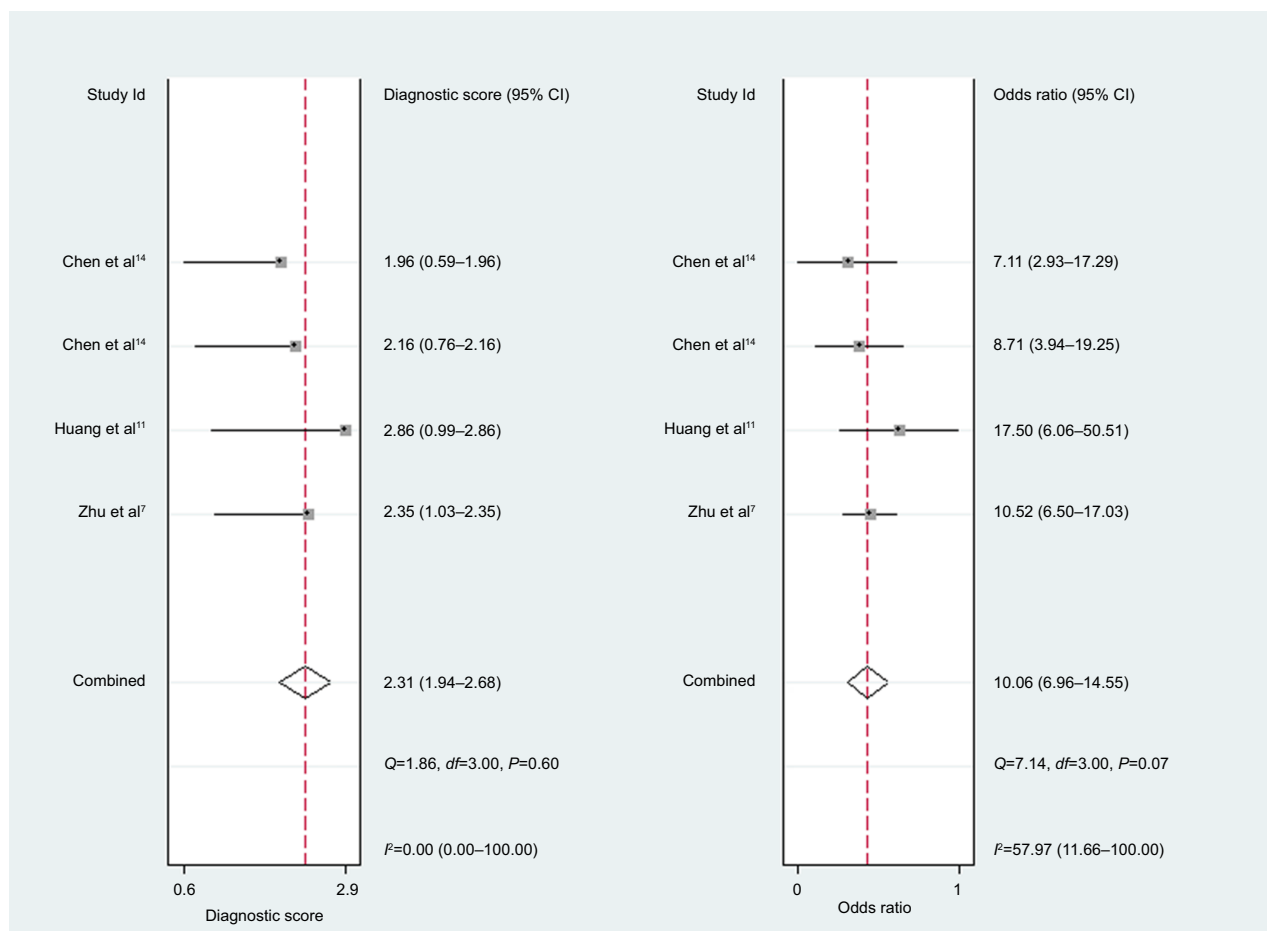**Abbreviation:** DLR, diagnostic likelihood ratio.

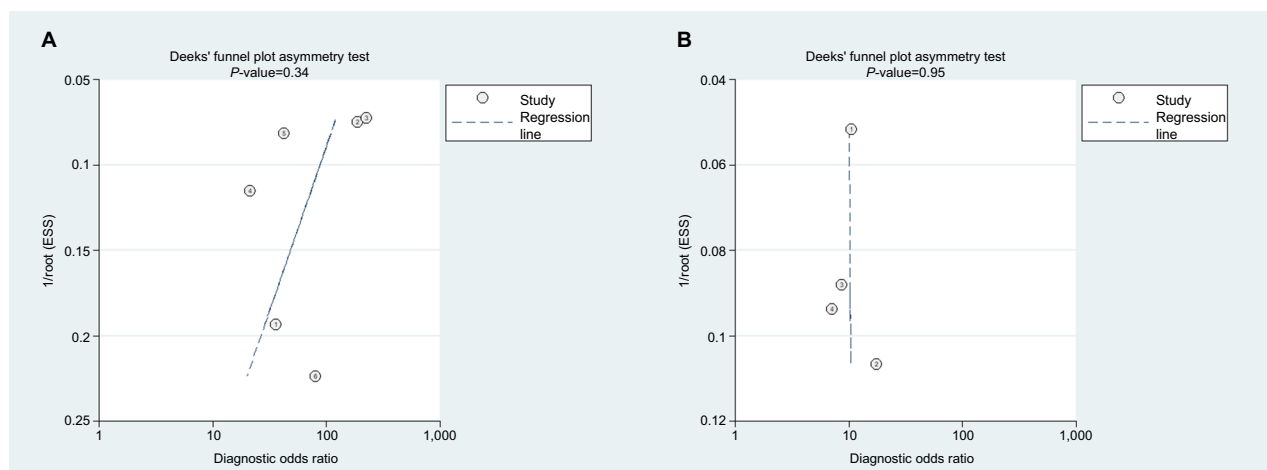**Figure 10** Forest plots of diagnostic score and diagnostic odds ratio for miR-30c.

Figure 11 Deeks' funnel plots.
Note: (**A**) miR-21, (**B**) miR-30c.

included studies. Although sensitivity analysis was carried out, it was still hard to identify which study was the source of heterogeneities.

Three previous meta-analyses (by Yin et al, Ouyang et al, and Yang et al) also reported the diagnostic value of

microRNAs for PCa,[18–20] we read them carefully with great interest. The number for miR-21 of enrolled studies by a previous meta-analysis (by Yin)[18] was less than our meta-analysis. Other two meta-analyses (by Ouyang et al and Yang et al)[19,20] only focused on overall microRNAs but not each

single microRNA, inevitably brought about significant heterogeneities, lower quality assessments, and meaninglessness in application. Another previous meta-analysis by Song et al provided mean ± SD or fold change of microRNAs expression levels in PCa patients vs controls,[21] but did not provide diagnostic information, such as pooled SEN and SPE.

Limitations

There were several limitations in our meta-analysis. First, the situation of unclear risk in the domains of patient selection and index could lower methodological qualities. Second, significant heterogeneities existed among included studies of miR-30c. Despite sensitive analysis being performed, potential sources of heterogeneities were still hard to been found. Third, comparison with blood-based specimen, tissue-based specimen is difficult to obtain in real life. Fourth, the number of included studies were few. It is necessary to adopt standardization of control group, specimen, and index test and to conducted more related studies.

Conclusion

Our meta-analysis showed that, for PCa, miR-21 is a good diagnostic biomarker and miR-30c is a moderate diagnostic biomarker.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 (Table S2)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5–6
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6–7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7–8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7–8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8

(Continued)

Table S1 (*Continued*)

DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8–9	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10	
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13	

Table S2 Search strategy

	Search strategy
#1	"microRNA" OR "miRNA" OR "miR" AND "prostate cancer" AND "diagnosis"
#2	"microRNA" OR "miRNA" OR "miR" AND "prostate cancer" AND "sensitivity"
#3	"microRNA" OR "miRNA" OR "miR" AND "prostate cancer" AND "specificity"
#4	"microRNA" OR "miRNA" OR "miR" AND "prostate carcinoma" AND "diagnosis"
#5	"microRNA" OR "miRNA" OR "miR" AND "prostate carcinoma" AND "sensitivity"
#6	"microRNA" OR "miRNA" OR "miR" AND "prostate carcinoma" AND "specificity"

Table S3 Sensitivity analysis for pooled sensitivities and corresponding heterogeneities

A			
Study[a]	**SEN (95% CI)**	**I^2 index (%)**	**P**[b]
Porzycki et al[1]	0.91(0.87–0.94)	0	0.43
Yang et al[2,c]	0.90 (0.85–0.94)	0	0.58
Yang et al[2,d]	0.90 (0.85–0.93)	0	0.75
Gao et al[3]	0.92 (0.88–0.95)	0	0.58
Huang et al[4]	0.92 (0.87–0.95)	0	0.61
Kotb et al[5]	0.91(0.88–0.94)	0	0.434
B			
Study[a]	**SEN (95% CI)**	**I^2 index (%)**	**P**[b]
Zhu et al[6]	0.73(0.66–0.79)	78.3	0.01
Huang et al[7]	0.72 (0.66–0.76)	71.3	0.03
Chen et al[8,c]	0.71 (0.65–0.76)	68.5	0.04
Chen et al[8,d]	0.76 (0.70–0.80)	33.4	0.22

Notes: (**A**) miR-21, (**B**) miR-30c. [a]Given named study is omitted. [b]P-value of the Cochrane-Q test. [c]Control group consisted of patients with benign prostate disease. [d]Control group consisted of healthy people.

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