

Review Article

Diagnostic value of microRNAs in prostate cancer patients: a meta-analysis

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Abstract: Background: The diagnostic performance of microRNAs (miRNAs) for the detection of prostate cancer (PCa) has not yet been validated. Here, we performed a meta-analysis to assess the diagnostic value of miRNAs as biomarkers for PCa. Methods: A systematic literature search was performed using the PubMed, Embase, and Web of Science databases between 2011 and 2016 to identify relevant publications. Fixed-effect or random-effect models were used to estimate pooled odds ratios (ORs), sensitivity (SENS), specificity (SPEC), diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR), area under curve (AUC), and the corresponding 95% confidence intervals (CIs). Results: Eight articles containing ten studies (case-controlled) were included in this meta-analysis. The pooled OR for prostate cancer was 20.01 (95% CI: 14.17-28.26), SENS was 0.91 (95% CI: 0.86-0.94), SPEC was 0.68 (95% CI: 0.60-0.76), DOR was 21 (95% CI: 14-21), PLR was 2.9 (95% CI: 2.3-2.6), NLR was 0.14 (95% CI: 0.10-0.19), and AUC was 0.88 (95% CI: 0.85-0.91). Conclusion: The results of meta-analysis support the diagnostic value of detecting miRNA concentration in patients with PCa, although additional evidence is necessary to validate these conclusions before development of miRNAs as clinical diagnostic biomarkers.

Keywords: Diagnosis, microRNAs, prostate cancer, meta-analysis

Introduction

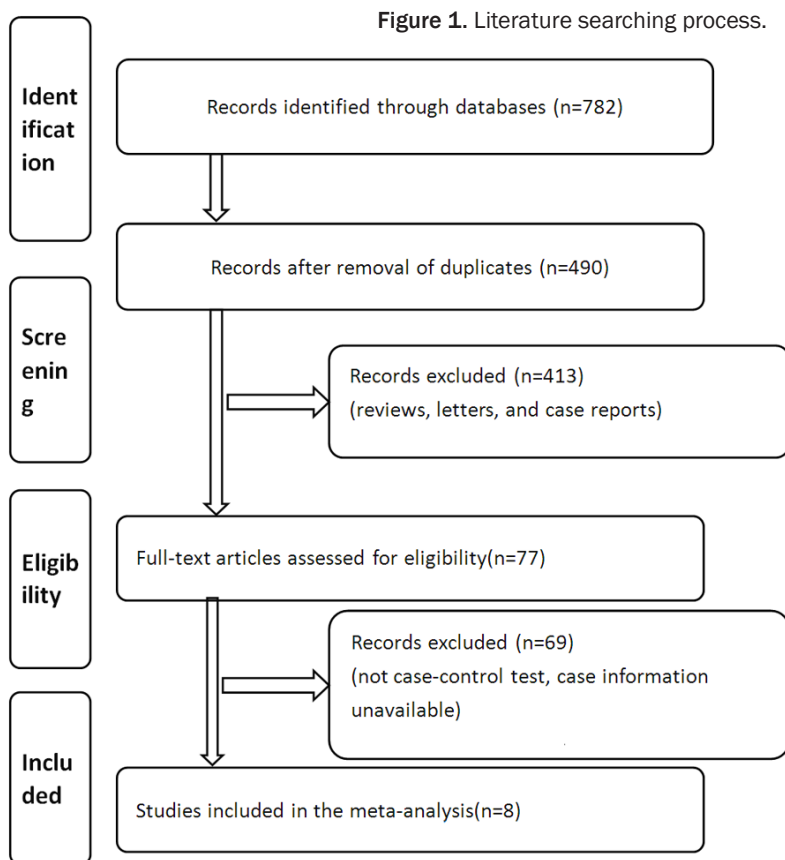
Despite the recent decline in the incidence of prostate cancer (PCa) [1], it remains the most common cancer in men and the fourth most common carcinoma worldwide [2]. PCa is the most frequently diagnosed malignancy among men in developed countries, where the incidence rates can be several times higher than those in less developed countries. In 2016, 1,111,700 new cases of PCa and 307,500 deaths are estimated worldwide [1]. Multiple genetic and demographic factors, including family history, age, and race, affect the incidence of PCa [3]. The identification of diagnostic and prognostic biomarkers for PCa is important to facilitate the diagnosis of PCa and to predict its prognosis.

MicroRNAs (miRNAs) are small noncoding RNAs that modulate gene expression at the post-transcriptional level by targeting mRNAs, allowing regulation by the silencing of translation and expression [4]. Studies show that miRNAs are associated with almost all biological path-

ways, including cell proliferation, apoptosis, phagocytosis, differentiation, and autophagy [5, 6]. Additionally, miRNAs play a key role in regulating tumorigenesis and promoting tumor development and progress (migration and invasion) [6-8].

Circulating miRNAs provide information about distinct tumor biology in individual patients [9-11]. *Mitchell* first proposed using circulating miRNAs as blood or serum biomarkers for diagnosis of PCa because of their stability [12]. MiRNA-141 is upregulated in the serum of men with PCa, as are miR-129, miR-187, miR-182, and miR-100. Increasing evidence indicates changes in the levels of miRNAs can be utilized in the diagnosis and prognosis of primary and advanced PCa [13-16]. To identify circulating miRNAs associated with PCa, we performed a meta-analysis by collecting data based on whole blood or serum and urine miRNAs from PCa patients with histopathology data and evaluated the significance of miRNAs as effective diagnostic markers in PCa.

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vided; (e) miRNA microarray measurement was performed and the data was provided clearly. Exclusion criteria were (a) duplicate articles or data; (b) review articles, editorial comments, letters, or case reports; (c) non-human models; (d) full text unavailable even contacted the correspondent author; (e) cohort studies were not included in this study.

Assessment of methodological quality

Two investigators systematically assessed the quality of each article found in the literature search to determine if it should be included in the meta-analysis using the nine-star Newcastle-Ottawa scale [17]. The studies were assessed according to eight items grouped into three broad

Materials and methods

Publication search

The PubMed, Embase, and Web of Science databases were searched between 2011 and 2016 using the terms “prostate cancer/carcinoma/tumor/neoplasms” and “microRNA or miR”. Without language restrictions, two or three investigators conducted the search and determined relevance of the identified studies. Any differences were checked and resolved by discussion. References of the identified articles were also searched for other relevant publications.

Inclusion criteria and exclusion criteria

For inclusion in this meta-analysis, studies had to meet the following criteria: (a) the study was designed as a case-control study; (b) PCa was diagnosed histopathologically; (c) the first author, published year, samples size, specimen type and diagnostic microRNAs about the study population was included; (d) a clear description of the study and outcome assessment was pro-

spective, including selection, comparability, and outcome for case-control studies. A score of 7 points (range 0 to 9 points) was considered high quality. Discrepancies were resolved by discussion to reach a consensus result.

Data extraction

Data was independently extracted from each study by two investigators. Discrepancies were adjudicated by a third investigator until consensus was reached on each item. Data extracted from each study included the name of the first author, year of publication, country of origin, type of miRNA, case and control sample size, sensitivity, and specificity, with the corresponding 95% CIs for each study. The true positive (TP), false positive (FP), false negative (FN), true negative (TN) cases were extracted according to the following formula: $SENS=TP/(TP+FN)$, $SPEC=TN/(TN+FP)$.

Statistical analysis

This meta-analysis was performed using Stata 14.0 (College Station, Texas, USA), and the sta-

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Table 1. Summary of included studies

Author	Year	Country	Territory	MicroRNAs	Specimen	Patients	Controls	Sens	Spec	tp	fp	fn	tn	AUC	Methods	Level
Salido-Guadarrama [27]	2016	Mexico	America	miR-100/200b	Urine	73	70	0.822	0.814	60	13	13	57	0.876	TaqMan	Up
Xu [29]	2015	China	Asia	miR-129	Blood	98	56	0.889	0.667	72	26	9	47	0.846	SYBR	Down
Kelly (1) [25]	2015	Ireland	Europe	miR-141	Serum	75	27	0.94	0.53	55	20	4	23	0.655	TaqMan	Up
Kelly (2) [25]	2015	Ireland	Europe	let-7a	Serum	75	27	0.93	0.51	53	22	4	23	0.678	TaqMan	Down
Kelly (3) [25]	2015	Ireland	Europe	let-7a, miR-141/145/155	Serum	75	27	0.97	0.63	60	15	2	25	0.8	TaqMan	*
Kachakova [24]	2015	Bulgaria	Europe	let-7c, miR-141	Serum	59	27	0.77	0.73	54	5	16	11	0.753	SYBR	Down
Huang [22]	2015	China	Asia	miR-21	Blood	75	75	0.875	0.857	63	12	9	66	0.833	TaqMan	Up
Kristensen [26]	2014	Sweden	Europe	miR-452/224	Blood	245	35	0.955	0.943	233	12	11	24	0.98	TaqMan	Down
Casanova-Salas [23]	2014	Spain	Europe	miR-182/187	Tissue	50	10	0.886	0.5	47	3	6	4	0.711	TaqMan	Up
Srivastava [28]	2013	USA	America	miR-205/214	Urine	36	12	0.89	0.8	32	4	4	8	0.87	TaqMan	Down

(tp: true-positive, fp: false-positive, fn: false-negative, tn: true-negative). *Not provided.

Table 2. Subgroup meta-analysis (divided by methods, levels or specimen)

Subgroup	Factor	Heterogeneity (OR)	SENS (95% CI)	SPEC (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
Methods	Taqman (n=8)	$I^2=0.0\%$, $P=0.55$	0.92 (0.88-0.95)	0.68 (0.58-0.77)	2.9 (2.2-3.9)	0.12 (0.08-0.16)	24.56 (16.50-36.56)	0.91 (0.88-0.93)
	SYBR (n=2)	$I^2=0.0\%$, $P=0.37$	0.83 (0.77-0.89)	0.65 (0.54-0.75)	2.49 (1.86-3.34)	0.24 (0.12-0.50)	11.59 (5.82-23.08)	*
	Pooled	$I^2=11.5\%$, $P=0.34$	0.91 (0.86-0.94)	0.68 (0.60-0.76)	2.9 (2.3-3.6)	0.14 (0.10-0.19)	20.22 (13.95-29.29)	0.88 (0.85-0.91)
Levels	Up-regulated (n=4)	$I^2=0.0\%$, $P=0.485$	0.88 (0.83-0.91)	0.76 (0.69-0.82)	3.24 (1.79-5.87)	0.18 (0.13-0.25)	22.25 (13.13-37.71)	0.91 (0.88-0.93)
	Down-regulated (n=5)	$I^2=33.3\%$, $P=0.200$	0.91 (0.88-0.93)	0.62 (0.55-0.69)	2.31 (1.92-2.79)	0.16 (0.08-0.29)	16.86 (9.27-30.68)	0.77 (0.70-0.84)
	Pooled	$I^2=9.4\%$, $P=0.357$	0.90 (0.87-0.92)	0.69 (0.64-0.74)	2.72 (2.10-3.53)	0.16 (0.12-0.23)	19.25 (13.24-28.00)	0.88 (0.86-0.90)
Specimen	Blood (n=3)	$I^2=45.2\%$, $P=0.161$	0.93 (0.90-0.95)	0.73 (0.66-0.79)	3.32 (2.07-5.34)	0.12 (0.07-0.22)	28.02 (13.92-56.38)	0.91 (0.86-0.96)
	Serum (n=4)	$I^2=19.5\%$, $P=0.293$	0.90 (0.85-0.93)	0.57 (0.48-0.65)	2.11 (1.74-2.55)	0.15 (0.06-0.36)	15.22 (7.56-30.63)	0.76 (0.67-0.85)
	Urine (n=2)	$I^2=0.0\%$, $P=0.798$	0.84 (0.76-0.91)	0.79 (0.69-0.87)	3.81 (2.42-6.00)	0.21 (0.13-0.33)	19.21 (9.08-40.63)	*
	Pooled	$I^2=16.5\%$, $P=0.296$	0.90 (0.88-0.92)	0.69 (0.64-0.73)	2.74 (2.16-3.48)	0.15 (0.10-0.22)	20.81 (14.09-30.74)	0.88 (0.86-0.90)

*number of quadrature points is greater than the number of observations. Cutoff value: 0.75.

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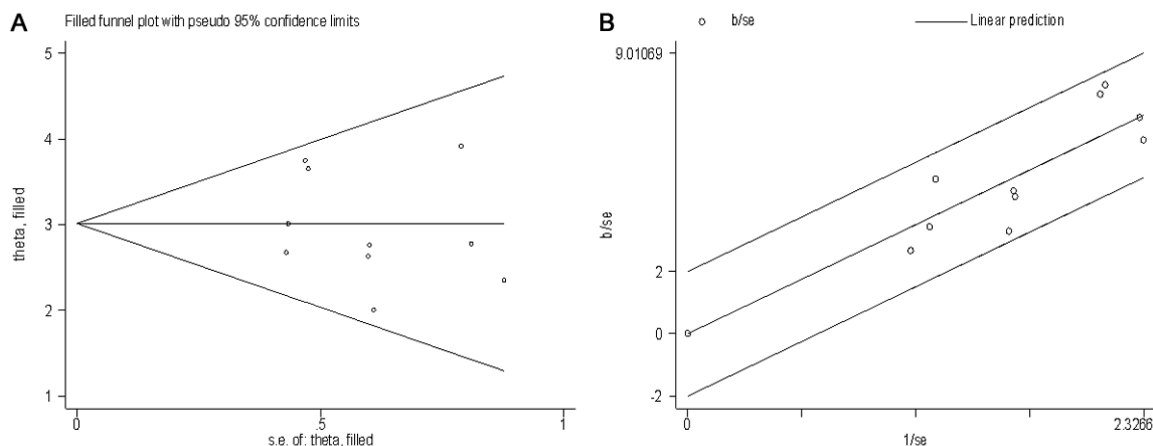


Figure 2. Plots of publication bias and Heterogeneity test. A: Trim and fill funnel plot. The filled diamonds represent one presumed missing study. B: Heterogeneity test: Galbraith plot.

tistical analysis was performed using Mantel-Haenszel fixed-effects or DerSimonian-Laird random-effects models to assess statistical heterogeneity. The corresponding 95% CIs were calculated and P values of less than 5% ($P < 0.05$) were considered significant.

The measures of the meta-analysis included ORs, SENS, SPEC, diagnostic ratios, the summary ROC (SROC) curve, and the AUC. For the AUC, values close to 1.0 indicated good diagnostic methods. A forest plot was generated to display the results and the Begg's and Egger's tests were performed to detect publication bias. The influence of publication bias on the overall effect was assessed by the "trim and fill" method introduced by Duval *et al* [18]. A statistic for measuring heterogeneity was calculated using the Q and I^2 method ($I^2 < 50\%$ was considered low-level heterogeneity and $I^2 > 50\%$ was considered high-level heterogeneity) [19, 20].

Results

Summary of the included studies

As showed in **Figure 1**, of 728 published records initially retrieved from the PubMed, EMBASE, and Web of Science databases, 292 were excluded because of duplication. After the removal of reviews, letters, and case reports, 77 full articles were read carefully and 67 articles were then removed based on the exclusion criteria. Of the remaining 10 candidate articles, two were eliminated because the corresponding authors were contacted without response [15, 21]. Finally, eight articles were taken in

account in the meta-analysis, for 807 prostate cancer cases and 420 non-cancer cases (healthy control or benign prostate hyperplasia) from ten individual studies (**Table 1**) [22-29].

The characteristics of the included studies are listed in **Table 1**. These studies investigated 1227 cases from Asia, Europe, and America. MiRNA expression was measured by quantitative real-time polymerase chain reaction from PCa patients' urine, serum or blood in all studies. The cut-off values of miRNAs were different in each study.

Publication bias and heterogeneity test

Publication bias between the included studies was assessed ($P=0.248$), and Begg and Egger tests were performed to assess for publication and other small study biases. The results of the Begg test ($z=-0.63$, $P=0.53$) and Egger regression analysis ($t=-0.66$, $P=0.53$) are shown as indicated. The results of the trim-fill plot (**Figure 2A**) showed no publication bias. Overall, these results revealed no evidence of publication/small-study bias in the comparisons.

The forest plot of the included studies showed that heterogeneity chi-squared ($\chi^2=10.17$; $P=0.0337$; $I^2=11.5$) (**Figure 4**), and heterogeneity test Galbraith plot (**Figure 2B**) showed no evidence of heterogeneity among the included studies.

Sensitivity and specificity analyses

The sensitivity (SENS) and specificity (SPEC) of the meta-analysis are important parameters to

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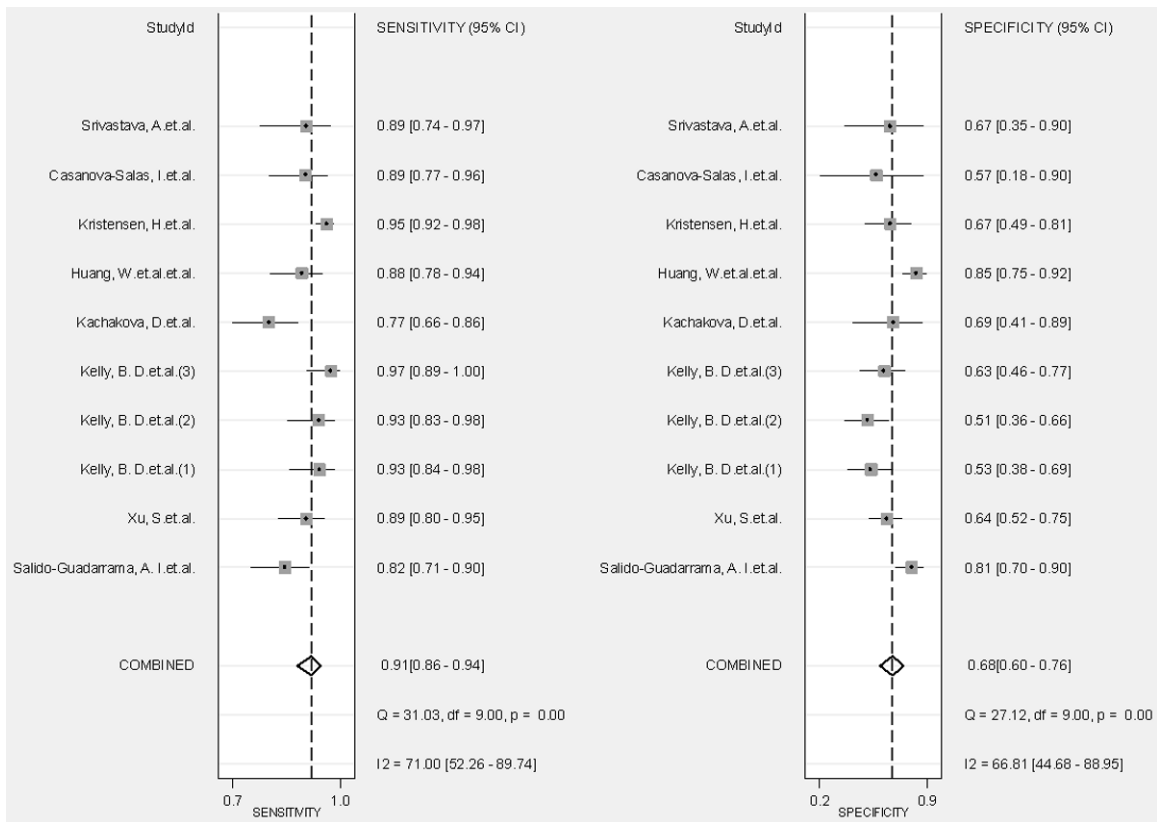


Figure 3. Sensitivity and specificity. SENS=0.91 (0.86-0.94), $I^2=71.00$, $P=0.00$; SPEC=0.68 (0.60-0.76), $I^2=66.81$, $P=0.00$.

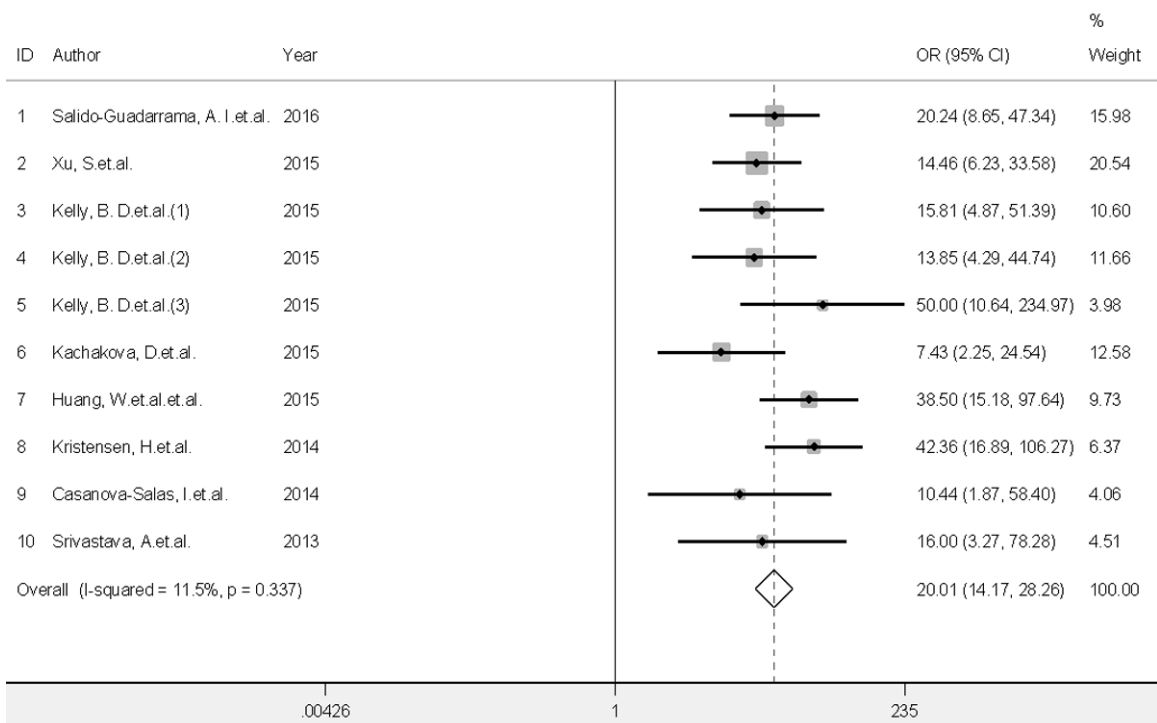


Figure 4. Forest plot of patients and control by odds ratios. Squares indicate study-specific odds ratios (size of the square reflects the study-specific statistical weight); horizontal lines represent 95% CIs; the diamond indicates the summary odds ratios estimate with its 95% CI.

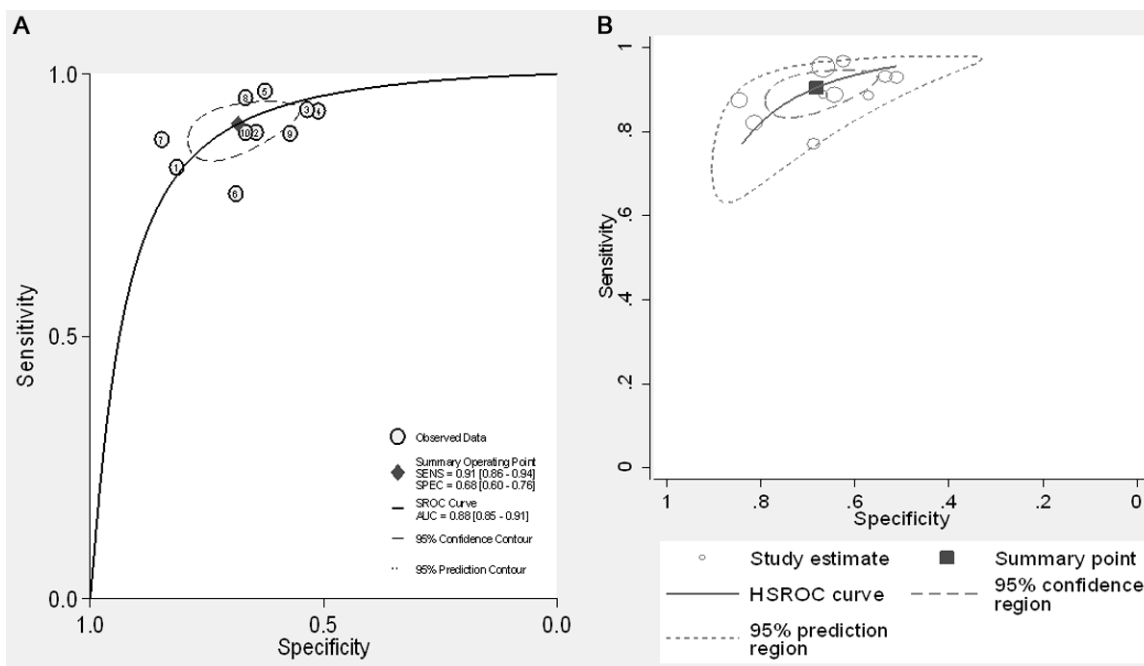


Figure 5. A: SROC: summary receiver operator characteristic curve. B: HSROC: hierarchical summary receiver operator characteristic curve.

assess the diagnostic method for patients with PCa. Our results showed high sensitivity at 0.91 (95% confidence interval (CI), 0.86-0.94) but poor specificity at 0.68 (95% CI, 0.60-0.76) due to significant heterogeneity (**Figure 3**) among the included studies.

Subgroup and meta-regression analyses were performed to examine this heterogeneity. In the subgroup analysis of PCa, no reason was found to explain the high heterogeneity of the SENS/SPEC. However, a high positive likelihood ratio of 2.9 (95% CI 2.3-3.6) indicated a better diagnosis of patients with PCa. The diagnostic odds ratio (OR) reached 21 (95% CI 14-31), indicating the significance of this diagnostic method for some PCa patients.

Meta-analysis results

Compared with control patients, the pooled OR and the corresponding 95% CI of PCa patients was 20.01 (95% CI: 14.17-28.26) (**Figure 4**), the SENS was 0.91 (95% CI: 0.86-0.94), the SPEC was 0.68 (95% CI: 0.60-0.76) (**Figure 3**), the diagnostic odds ratio (DOR) was 21 (95% CI: 14-21), the positive likelihood ratio (PLR) was 2.9 (95% CI: 2.3-2.6), the negative likelihood ratio (NLR) was 0.14 (95% CI: 0.10-0.19) (**Table 2**), and the area under the curve (AUC)

was 0.88 (95% CI: 0.85-0.91) (**Figure 5A**). The proportion of heterogeneity was likely due to the threshold effect ($P=0.70$), and the hierarchical summary receiver operator characteristic (HSROC **Figure 5B**) curve plot showed the following results: SENS=0.905 (95% CI: 0.862-0.936), SPEC=0.683 (95% CI: 0.598-0.757), PLR=2.85 (95% CI: 2.26-3.61), NLR=0.14 (95% CI: 0.10-0.19), and DOR=20.56 (95% CI: 13.8-30.60). These results support the reliability of the meta-analysis and its outcome.

Subgroup meta-analysis results

Next, we investigated the effects of the miRNA detection method (SYBR or Taqman), miRNA expression pattern (up-regulated or down-regulated), and the specimen type on the diagnostic significance of miRNAs. The results of the analysis (**Table 2**) showed that miRNAs in the blood and down-regulated miRNAs exhibited moderate heterogeneity. These differences could be resulted from differences in the RNA extraction methods, blood products, or the use of various endogenous controls. There is evidence that RNase activity is increased in the serum of PCa patients [30]. An additional complication is that the miR-141 expression pattern differs between studies, as miR-141 was found to be up-regu-

lated in Kelly [31], but was reported to be down-regulated in the study by Kachakova et al [24].

Discussion

There are limited studies examining the diagnostic performance of miRNAs in PCa. This meta-analysis is limited because it included only a small number of studies, and these were often limited by a lack of details included in the original publication. We emailed the corresponding authors of the original papers to obtain additional details; however, two authors failed to provide additional information [15, 21]. In addition, two studies were contradictory, with the studies by Kelly et al [31] and Kachakova et al [24] reporting opposite results for the pattern of expression of miR-141. These limitations affected the heterogeneity, publication bias, SENS, SPEC, DOR, and AUC of our analysis. Finally, the false-positive rate was not very obvious between PCa and the controls, and this decreased the statistical power of the study.

Recently, a series of quantitative analyses were performed to assess the diagnostic potential of miRNAs in various cancers. Wang *et al* demonstrated that altered miRNAs can be used as novel biomarkers for the early detection of gastric cancer [32]. These authors identified 47 miRNAs that are aberrantly expressed in gastric cancer (29 up-regulated and 18 down-regulated) as reported in the literature. These authors conducted a meta-analysis to assess the diagnostic value of these altered miRNAs, and the pooled data showed good sensitivity and specificity and high overall accuracy. In other work, Zhang *et al* showed that a three-miRNA (miR-199a, miR-29c and miR-424) signature is a promising circulating biomarker for breast cancer diagnosis [31]. These three miRNAs exhibit high diagnostic accuracy for discriminating breast cancer patients from healthy controls and ROC curve analysis was successfully confirmed in the validation set.

Multiple studies suggest that miRNAs play an essential role in distinguishing PCa from normal patients [15, 22, 23, 25, 29]. As mentioned previously, miR-100/200b, miR-21, and miR-182/187 are significantly up-regulated in PCa. In contrast, miR-129, let-7a, let-7c, miR-452/224, and miR-205/241 are significantly down-regulated in PCa. Therefore, we conducted a pooled meta-analysis and a subgroup meta-

analysis to investigate the diagnostic relevance of miRNAs in PCa. Our results indicated high diagnostic sensitivity and DOR, highlighting the effectiveness of miRNAs as diagnostic markers for PCa.

In summary, the findings of this meta-analysis of 10 studies suggest the diagnostic value of miRNA concentrations in the blood or urine in patients with PCa. Our results (high sensitivity and high DOR) indicate that miRNAs may be effective as biomarkers for the diagnosis of PCa. In future work, we plan to collect additional clinical case-control studies to increase the scope of the analysis and improve our understanding of the diagnostic performance of miRNAs to help clinicians improve the accuracy of PCa diagnosis.

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Disclosure of conflict of interest

None.

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