Meta-analysis of microRNAs as biomarkers for muscle-invasive bladder cancer

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Abstract. Bladder cancer is the most common cancer of the urinary tract. A quarter of bladder cancer patients presenting with muscle-invasive bladder cancer (MIBC) suffer significant morbidity and succumb to the disease. MicroRNA (miRNA) from tissue, urine or blood samples of MIBC patients have been demonstrated to differ from healthy individuals, and possibly have diagnostic value. The aim of the present meta-analysis was to access the overall diagnostic accuracy comprehensively and quantitatively. Systematic searching in PubMed, Web of Science, Embase and Chinese National Knowledge Infrastructure database was conducted. The pooled sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR) and diagnostic odds ratio (DOR) were calculated via the random effects model to evaluate the overall test performance. Deeks' funnel plot asymmetry test was used to test the publication bias. A total of 10 studies were included in the meta-analysis, with a total of 577 patients and 412 controls. The pooled sensitivity and specificity were 0.78 [95% confidence interval (CI), 0.69-0.86] and 0.77 (95% CI, 0.72-0.81), respectively. The pooled PLR was 2.9 (95% CI, 2.1-3.8), the NLR was 0.31 (95% CI, 0.27-0.35), the DOR was 7 (95% CI, 4-13) and the pooled AUC was 0.80 (95% CI, 0.69-0.87). In conclusion, the current miRNA assays support their use as markers for MIBC diagnosis.

Introduction

Bladder cancer is one of the most common cancer ranking fourth in incidence in Western countries and first in China (1,2). There are ~380,000 new cases and 150,000 fatalities per year worldwide (3). Bladder cancer is staged via the tumor-node-metastasis system, which describes the extent of invasion (Tis-T4) (4,5). Approximately 75% of patients present with non-invasive bladder cancer (NIBC; stage Ta), but a quarter suffer muscle-invasive bladder cancer (MIBC) at the time of diagnosis (of stage T2 and above) and they have a less favorable prognosis with 5-year survival <50% (6,7). Despite improvements in surgical techniques and postoperative recovery pathways, this complex procedure remains highly challenging, and the treatment has not advanced for several decades (8,9). Furthermore, the high cost of surgery and management of subsequent complications, chemotherapy, surveillance imaging and high end-of-life costs contribute to the substantial financial burden of advanced disease (10). Therefore, development of early biological markers for diagnosis of MIBC is of importance.

MicroRNA (miRNA) is endogenous RNA of ~22 nucleotides that targets mRNA for cleavage or translational repression. miRNA families are responsible for a number of physiological processes, including cell growth/differentiation, maintenance of internal environmental stabilization, immune response and embryonic development of different cancers (11-14). Increasing evidence has suggested that miRNAs can be transmitted through extracellular vesicles, such as exosomes, that are devoted to cell-cell contact and influence, and additionally they are convenient for detection (15,16). Thus far, various miRNAs have been identified to have prognostic values with bladder cancer, in NIBC and MIBC (17-19).

Currently, there are few meta-analyses published on the diagnostic performance of miRNA assays for MIBC. Therefore, the present study performed a meta-analysis to review and assess the overall diagnostic values of miRNA assays for MIBC.

Materials and methods

Publication search. To identify all the potentially eligible studies on miRNA polymorphisms and cancer risk, we carried out a systematic search on PubMed, Web of Science and Chinese National Knowledge Infrastructure, covering all studies published between January 1, 2000 and January 25, 2016, using the search terms: ('miR' or 'miRNAs' or 'microRNAs') and ('diagnostic value' or 'diagnoses' or 'receiver operating characteristics' or 'ROC curve' or 'sensitivity and specificity')

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Abbreviations: MIBC, muscle-invasive bladder cancer; NIBC, non-invasive bladder cancer; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; SROC, summary receiver operator characteristic; SEN, sensitivity; SPE, specificity; AUC, area under SROC curve

and ('muscle-invasive bladder cancer, muscle-invasive urinary bladder neoplasms, muscle-invasive urothelial cancer, MIBC, MIUCC'). References of the retrieved studies and review studies were also screened. Qualified studies had to meet all the following standards: i) Diagnosis of MIBC in histology, ii) utility of miRNA expression profiles (from tissue or blood or urine) for urological cancers diagnosis. The exclusion criteria included: i) Reviews, case reports, and meta analyses, ii) studies not related to MIBC and the diagnostic value of miRNA for urological cancers, iii) studies without valid data.

Data extraction and quality assessment. Quality assessment was performed for each included study by independent reviewers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (20). The QUADAS-2 tool contains seven questions, and each one should be answered with 'yes' (1 score), 'unclear' or 'no' (0 score). All questions were given equal weight, resulting in a maximum possible score of 7. Conflicting evaluation was resolved following a full discussion.

The assessment consisted of four domains: Patient selection, index test, reference standard, and flow and timing. The first three domains were assessed in terms of applicability. Each of the four domains was assessed via the risk of bias. Assessments were labeled as 'high', 'low' or 'unclear', corresponding to high risk, low risk and unclear, respectively.

Statistical analysis. All the statistical analyses were performed using Rev Man 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The sensitivity and specificity data of miRNAs associated with the predicted and/or diagnostic value of MIBC were extracted from each study. First, the results of sensitivity, specificity, positive and negative likelihood ratio (PLR and NLR, respectively), diagnostic odds ratio (DOR) and 95% confidence intervals (CIs) were calculated using the random-effect model. Subsequently, the summary receiver operator characteristic (SROC) curve was created and the area under the SROC curve (AUC) was calculated. PLR was on behalf of the odds of positive test results of MIBC patients, while NLR reflected the odds of positive results in those without MIBC. DOR was the outcome of the combination of PLR and NLR (DOR = PLR/NLR). In addition, the heterogeneity between studies was evaluated through χ^2 test and I^2 test. If the tests show a P<0.1 or I^2>50%, the existence of significant heterogeneity would be verified (21). Subsequently, meta-regression and subgroup analyses were undertaken to explore the sources of between-study heterogeneity. Furthermore, Deeks' funnel plots were adopted to evaluate the publication bias.

The percentages of patients in each subgroup were calculated for the categorical variables using unpaired Student's t-test, χ^2 test or Fisher's exact test, appropriately.

Results

Patient characteristics. The flow graph of study selections is shown in Fig. 1. A total of 125 potentially relevant studies were selected with an established search strategy. Following a detailed evaluation, 10 studies (22-31) were used for the
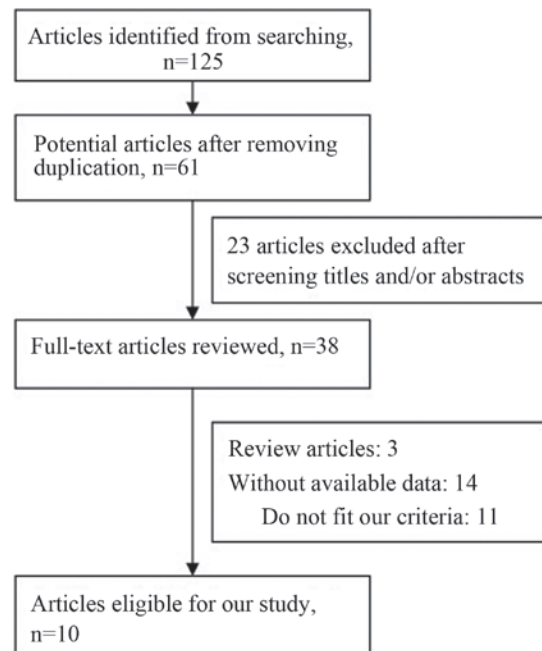

Figure 1. Flow chart of the included studies.

meta-analysis. The main characteristics of the included studies are summarized in Table I. Among the 10 studies, the total number of patients and controls were 577 and 412, respectively. Four studies were conducted in Asian populations, while the remaining studies were conducted in Caucasian populations. The diagnostic performances of single and multiple miRNAs have been investigated among those included studies.

Quality assessment of studies. The results of the QUADAS-2 assessment are shown as a bar graph in Fig. 2. The majority of all included studies fulfilled the majority of the items in QUADAS-2, which indicated that the general quality of the included studies is good.

Diagnostic accuracy. Due to the existence of significant heterogeneity between studies in sensitivity and specificity (I^2=81.3% and I^2=77.8%), the random effects model was adopted. Fig. 3 depicts the forest plots of data from the miRNA panels subgroup and mean sensitivity and specificity. The pooled results of diagnostic criteria and their 95% CIs are listed in Table II. The overall sensitivity, specificity, PLR, NLR and DOR were 0.78 (0.69-0.86), 0.77 (0.72-0.81), 2.9 (95% CI, 2.1-3.8), 0.31 (95% CI, 0.27-0.35), 7 (95% CI, 4-13), respectively. Moreover, the SROC curve was generated and the AUC was calculated as 0.80 (95% CI, 0.69-0.87) (Fig. 4), which implied a relatively high diagnostic accuracy.

Subgroup analyses. A subgroup analyses was also performed to identify potential sources of heterogeneity (Table II). For single miRNA profiling assays, sensitivity, specificity and AUC values were 0.70 (0.65-0.74), 0.73 (95% CI, 0.67-0.79), and 0.79 (95% CI, 0.76-0.82), respectively. For multiple miRNAs, the sensitivity (SEN), specificity (SPE) and AUC values were 0.81 (95% CI, 0.72-0.91), 0.84 (95% CI, 0.75-0.93) and 0.86 (95% CI, 0.83-0.89), respectively. These data indicated that multiple miRNAs profiling were more accurate

Table I. Main characteristics of the 10 studies included in the meta-analysis.

First author, year	Country	Ethnicity	Sample size, n		Mean age, year		Mean ratio, %		Control	Specimen	miRNA profiling	Regulated features	Score	Refs.
			Case	Control	Case	Control	Case	Control						
Veerla, 2009	Sweden	Caucasian	17	17	NA	NA	NA	NA	Normal	Tissue	miR-100, miR-125b, miR-199b, miR-222	Up	5	(22)
Pignot, 2012	France	Caucasian	80	11	70	67	78.8	79.5	Normal	Tissue	miR-9, miR-182, miR-200b; miR-1, miR-133a, miR-133b; miR-143, miR-145, miR-204; miR-199a, miR-199b, miR-1281	Up; Down; Down; Down	7	(23)
Pignot, 2012	France	Caucasian	21	5	68	66	90.5	100.0	Normal	Tissue	miR-19A, miR-20A, miR-92A	Up	6	(24)
Adam, 2013	Germany	Caucasian	10	18	62	55	70.0	46.0	Normal	Blood	miR-200b, miR-541, miR-566; miR-543, miR-544,; miR-604, miR-940-p; miR-33b, miR-92b,6; miR-1246, miR-182; miR-25, miR-148b, miR-487	Up; Up; Down; Down	7	(25)
Ratert, 2013	Germany	Caucasian	15	42	74	68	80.0	83.0	NMIBC, normal		miR-141, miR-205	Up	6	(26)
Li, 2014	China	Asian	15	15	NA	NA	NA	NA	Normal	Tissue	miR-34a	Up	5	(27)
Aygeris, 2015	Greece	Caucasian	45	39	NA	NA	84.3	NA	Normal	Tissue	miR-143, miR-145, miR-224	Up	5	(28)
Wang, 2015	China	Asian	144	169	NA	NA	68.2	NA	Normal	Urine	miR-124	Up	6	(29)
Xu, 2015	China	Asian	202	40	68	64	74.3	65.0	Normal	Tissue	let-7c, mir-125b-1; mir-193a, mir-99a	Up; Up	7	(30)
Fang, 2015	China	Asian	28	56	75	74	71.4	64.2	Normal	Tissue	mir-205	Up	6	(31)

miRNA, microRNA; NA, not available; NMIBC, non-muscle invasive bladder cancer.

Table II. Summary estimates of diagnostic criteria and the 95% confidence intervals (CIs).

Analysis	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
Ethnicity						
Caucasian	0.71 (0.66-0.75)	0.76 (0.67-0.83)	2.4 (2.0-2.8)	0.34 (0.22-0.46)	6 (4-11)	0.74 (0.69-0.78)
Asian	0.67 (0.63-0.72)	0.75 (0.73-0.82)	2.5 (2.1-3.0)	0.32 (0.21-0.42)	7 (5-12)	0.82 (0.77-0.86)
miRNA profiling						
Single miRNA	0.70 (0.65-0.74)	0.73 (0.67-0.79)	2.6 (2.3-2.9)	0.38 (0.29-0.47)	5 (3-10)	0.79 (0.76-0.82)
Multiple miRNA	0.81 (0.72-0.91)	0.84 (0.75-0.93)	4.2 (2.7-5.7)	0.26 (0.15-0.37)	16 (9-24)	0.86 (0.83-0.89)
Overall	0.78 (0.69-0.86)	0.77 (0.72-0.81)	2.9 (2.1-3.8)	0.31 (0.27-0.35)	7 (4-13)	0.80 (0.69-0.87)

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve; miRNA, microRNA.
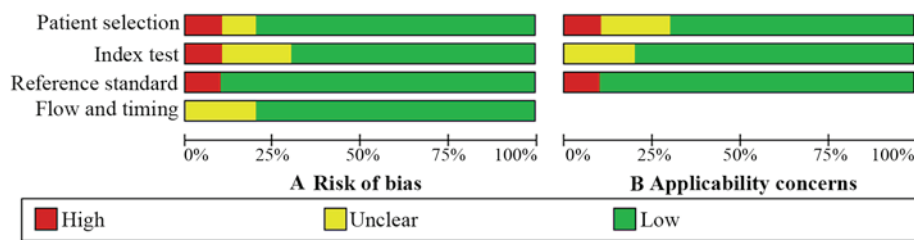

Figure 2. General assessment quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 tool.
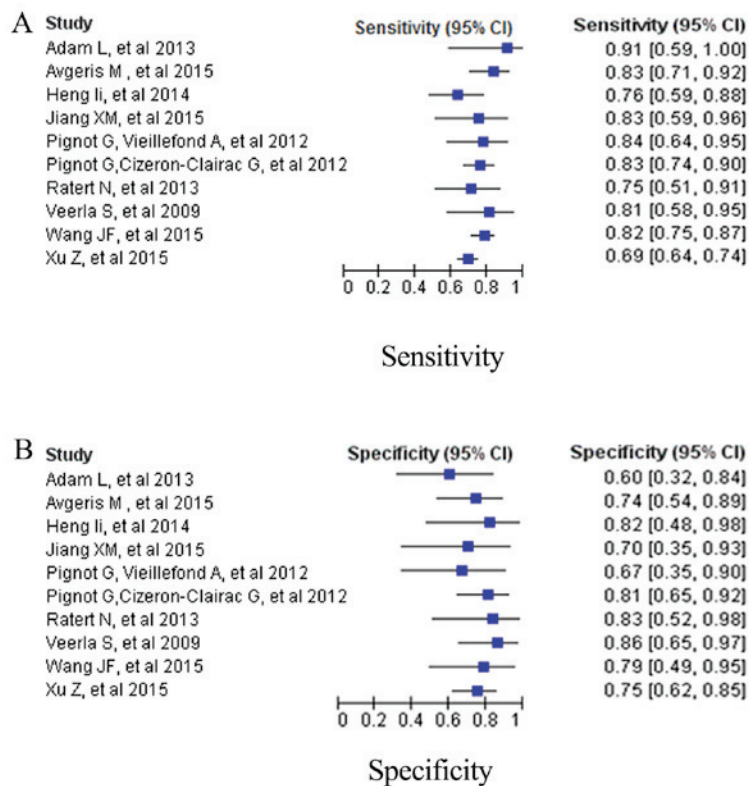

Figure 3. Forest plots of (A) sensitivity and (B) specificity of miRNAs for the miRNA panel subgroups. CI, confidence interval.

than single miRNA profiling. The studies based on Caucasian populations had a pooled sensitivity of 0.71 and a specificity of 0.76, while studies based on Asian populations had a relatively lower sensitivity (0.67) and specificity (0.75). The subgroup analyses suggested that the ethnicity and miRNA profiling had an evident influence on the diagnostic accuracy.
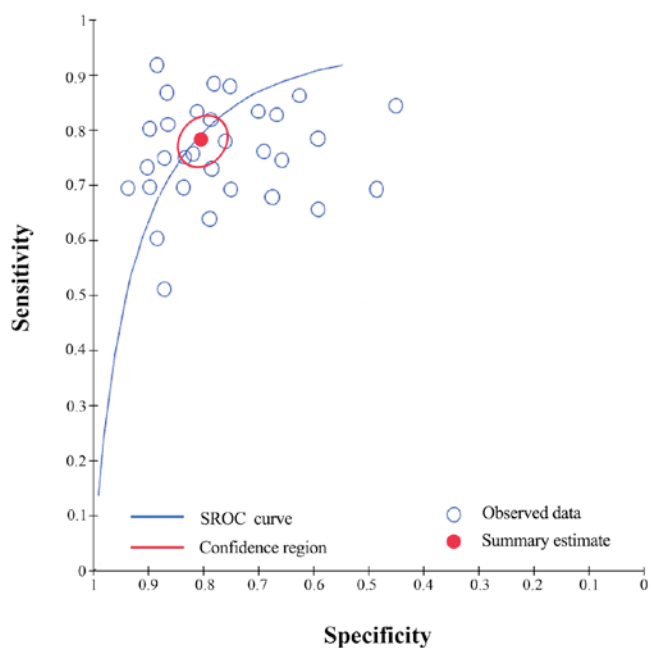
Figure 4. SROC curve of the studies with confidence and prediction region around mean operating sensitivity and specificity. SROC, summary receiver operator characteristic.
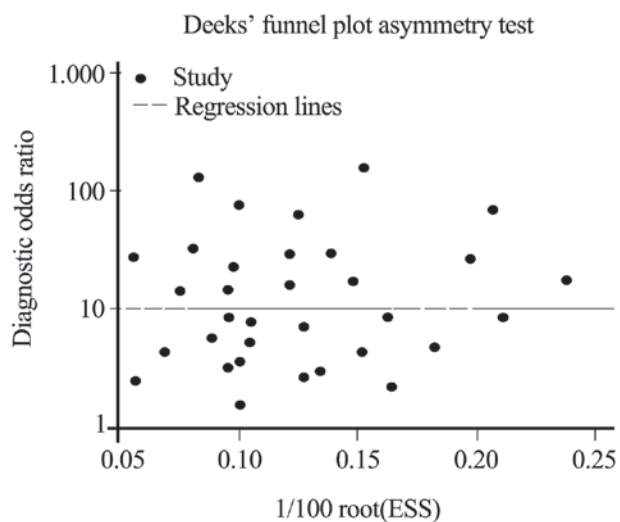

Figure 5. Deeks' linear regression test of funnel plot asymmetry. ESS, effective sample size.

Therefore, these factors may be the potential sources of heterogeneity.

Publication bias. Finally, the Deeks' funnel plot asymmetry test was conducted to evaluate the publication bias. The P-value of 0.7 suggested that no significant publication bias existed among the studies (Fig. 5).

Discussion

Although clear progression in surgery and chemical treatment has been achieved in MIBC, the prognosis of the patients is poor (6,7). As aforementioned, approximately a quarter of bladder cancer patients have MIBC at diagnosis, and the critical factor is how to detect and diagnose MIBC as early as possible. Thus, novel and reliable biomarkers for MIBC detection are urgently required.

As the existing biomarkers do not exhibit high sensitivity and specificity in MIBC detection, miRNAs have been reported as markers of MIBC in numerous studies. Pignot *et al* (23) reported that miR-9, miR-182 and miR-200b were associated with MIBC aggressiveness, and with recurrence-free and overall survival in univariate analysis and multivariate analysis. Avgeris *et al* (28) reported that high miR-143/145 levels could predict the inferior overall survival for MIBC effectively and the progression of superficial tumors independently. Xu *et al* (30) identified four specific miRNAs (let-7c, mir-125b-1, mir-193a, and mir-99a) in association with the progression and aggressiveness of MIBC via microarray analysis. Several genome-wide profiling studies have been reported and identified specific miRNA alterations in bladder cancer (32-34). Those results suggested a promising prognostic value of these miRNAs markers.

However, as the association between miRNAs and MIBC are inconsistent and the studies are designed differently, comparing the wide ranges of diagnostic performance is difficult. Therefore, the present study aimed to summarize the result of individual studies and investigate the diagnostic value of miRNAs for MIBC.

Following analysis, the overall sensitivity and specificity of miRNAs was 0.78 and 0.77, which indicated accuracy of miRNAs to detect MIBC. The pooled PLR was 2.9 and the pooled NLR was 0.31, respectively. The AUC was 0.80 and DOR was 7. These data suggested that miRNAs had a relatively high diagnostic accuracy. As heterogeneity between studies could affect the results of the meta-analysis, subgroup analyses will aid to understand these influences. Therefore, subgroup analyses were performed based on ethnicity and miRNA profiling. Subgroups of miRNA profiling indicated that multiple miRNA assays (SEN, SPE and AUC of 0.81, 0.84 and 0.86, respectively) had a higher diagnostic performance than those of single miRNA assays (SEN, SPE and AUC of 0.70, 0.73 and 0.79, respectively). No significant different was observed for the miRNA expression profile test between the Asian and Caucasian groups.

There were several limitations in the meta-analysis. First, the included studies were based on limited sample size, and if the specimen of miRNA could be divided into blood, urine, tissue groups, do analysis and comparison respectively, the results may be more significant and accurate. Second, the majority of the included studies did not differentiate the grade of MIBC, and therefore, subgroup analyses based on these variables were restricted due to limited reported data. Third, as the majority of the studies did not provide further miRNA research, the changes of miRNA in different stages of MIBC, following treatment in different methods or in patients who received treatment experiencing MIBC again could not be verified.

In conclusion, the present study analyzed the pooled data of SEN, SPE, PLR, NLR, DOR and AUC from 10 studies. miRNA assays could serve as markers for MIBC diagnosis, particularly the combined usage of miRNA, and have a good potential as an accurate biomarker to diagnose of MIBC. However, the clinical application of miRNA profiling for MIBC diagnosis remains validating in future studies.

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