The diagnostic value of miRNA-141 in prostate cancer
A systematic review and PRISMA-compliant meta-analysis
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Abstract
Background: miR-141 has gradually demonstrated its value in the diagnosis of prostate cancer. However, the diagnostic parameters in previous studies differ. A systematic review was conducted to explore the diagnostic value of miR-141 in prostate cancer.
Methods: A comprehensive search of the literature in the PubMed, Medline, Cochrane Library, and Embase databases was performed. The included 7 studies assessed the diagnostic value of miR-141 in patients with prostate cancer up to October 31, 2019. We used meta-disc version 1.4 and STATA software version 12.0 to analyze the data.
Results: The pooled sensitivity and specificity were 0.70 (95% confidence interval [CI] 0.64–0.75) and 0.73 (95% CI 0.64–0.80), respectively. The positive likelihood ratio was 2.88 (95% CI 1.40–5.93), and the negative likelihood ratio was 0.38 (95% CI 0.20–0.71). Further, we note that the pooled diagnostic odds ratio of miR-141 for prostate cancer was 9.94 (95% CI: 2.55–38.80). The summary area under the receiver operating characteristic curve was 0.83 (95% CI: 0.79–0.86). The results of meta-regression suggested that heterogeneity was mainly derived from patient age. The results of the Fagan nomogram showed that it was increased significantly by testing miR-141 for diagnosing prostate cancer.
Conclusion: This meta-analysis suggests that miR-141 has a high diagnostic value for prostate cancer. In the future, large-scale prospective studies are needed to verify and evaluate this result.
Abbreviations: AUC = area under SROC, CI = confidence interval, DOR = diagnostic odds ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SROC = summary receiver operating characteristic curve.
Keywords: meta-analysis, miR-141, prostate cancer

1. Introduction
Prostate cancer (PCa) is one of the most common malignant tumors of the male urinary system. In the European and American populations, its incidence rate ranks first, and its death rate ranks second.[1,2] More than 50% of patients are in an advanced stage or have metastasis when they are diagnosed, which seriously affects their prognosis and quality of life.[3] However, due to poor sensitivity or specificity, it is difficult for the current clinical selection of prostate-specific antigen and other markers to meet clinical needs.[4] Therefore, identifying a tumor marker with good sensitivity and specificity is important in the clinical diagnosis and treatment of PCa.

miRNAs are involved in the regulation of many cellular processes, including the occurrence of tumors.[5] A large number of studies have confirmed the differential expression of miRNA in tumor tissues, suggesting that the miRNA expression profiles can be used as a biomarker for the early detection, classification, and prognosis of tumors.[6,7] A previous study found that the miRNA expression profile was consistent with the clinicopathological data and had better accuracy in distinguishing tumor tissues from normal tissues.[8] Moreover, miRNA has high stability, which makes it a good diagnostic tumor marker.[9] In recent years, miR-141 has gradually demonstrated its value in the diagnosis of PCa and has become a potential new diagnostic marker.[10] However, the diagnostic parameters varied among previous studies.[11] Therefore, a systematic review was conducted to explore the diagnostic value of miR-141 in PCa.

2. Methods
2.1. Search strategy
We performed a meta-analysis in accordance with the guidelines of the preferred reporting items for systematic reviews and meta-
A comprehensive search of the literature in the PubMed, Medline, Cochrane Library, and Embase databases up to October 31, 2019 was performed. The following search strategy was used: (“microRNA-141” OR “miRNA-141” OR “miR-141” OR “CTC”) and (“prostate cancer” OR “prostate carcinoma” OR “prostate neoplasm” OR “prostate tumor”). Subsequently, eligible studies were included for further screening.

2.2. Study selection
Two researchers (Li and Wang) independently performed the literature search and study selection. Any disagreements were resolved by group discussion until a consensus was reached. Studies were included if they met the following study inclusion criteria:

1. miR-141 was involved in the study of patients who were diagnosed with PCa;
2. patients with PCa must be confirmed by pathological biopsy;
3. serum, plasma, or urine samples from patients with PCa were used, and the control group involved patients with benign prostate disease or healthy people; and
4. sensitivity, specificity, and critical values must be explicitly mentioned in the literature.

The exclusion criteria were as follows:

1. reviews, comments, letters, and articles with an indefinite diagnostic threshold;
2. incomplete clinical data for extraction;
3. duplicate records; and
4. experiments on animals or cell lines.

2.3. Data extraction
We collected the data from the included studies and extracted the following items: first author, publication year, country in which the study was performed, age, sample number, sample type, detection method for miR-141, the area under the receiver operating characteristic curve (AUC), and the sensitivity and specificity of miR-141 for diagnosing PCa.

2.4. Quality assessment
We used the quality assessment of diagnostic accuracy studies-2 tool to evaluate the quality of the studies included in this meta-analysis, which was performed independently by the 2 authors (Ye and Li). The method consisted of 4 components: patient selection, index test, reference standard, and flow and timing. The risk of bias for each item in individual studies can be judged as “low,” “high” or “unclear” and is summarized by proportion. All authors agreed to the final determinants of the literature to be considered. Because this is a systematic review and meta-analysis, the ethical approval and patient written informed consent are not required.

2.5. Statistical analysis
We used RevMan 5.3 to perform the quality assessment, and the statistical software Stata version 12.0 (Stata Corp LP, College Station, TX) and Meta-disc version 1.4 (version 1.4; Ramony Cajal Hospital, Madrid, Spain) were used to conduct other analyses. We calculated the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and corresponding 95% confidence intervals (95% CI) from true positive, false positive, false negative, and true negative cases, which were extracted from each study before data pooling. A bivariate random effects model was applied to summarize the sensitivity, specificity, PLR, NLR. A hierarchical regression model was used to summarize the summary receiver operating characteristic (sROC) curve and the area under the ROC. We used the Q statistic and I² to...
Table 1
Characteristics of the eligible studies in the meta-analysis.

| Author   | Year | Country | Case (control), n | Age | Method | Sample | AUC  | Sensitivity | Specificity |
|----------|------|---------|-------------------|-----|--------|--------|------|-------------|-------------|
| Pawel    | 2018 | Poland  | 20 (8)            | 68.6| PCR    | Serum  | 0.831| 65.0%       | 88.0%       |
| Darina   | 2015 | Bulgaria| 59 (27)           | 68  | PCR    | Plasma | 0.567| 56.5%       | 57.1%       |
| Christa  | 2014 | Denmark | 31 (13)           | –   | PCR    | Serum  | 0.580| 30.0%       | 100.0%      |
| Brian    | 2015 | Ireland | 79 (27)           | 64  | PCR    | Plasma | 0.655| 94.0%       | 70.0%       |
| Zhuo     | 2015 | China   | 20 (20)           | 69.5| PCR    | Serum  | 0.869| 80.0%       | 93.0%       |
| Nassin   | 2018 | Iran    | 23 (20)           | 68.4| PCR    | Urine  | 0.850| 88.0%       | 93.0%       |
| Fulya    | 2010 | Turkey  | 51 (20)           | 67  | PCR    | Serum  | 0.579| 65.0%       | 40.0%       |

AUC = area under curve, PCR = polymerase chain reaction.

Figure 2. Quality assessment of the included studies.
inspect the statistical heterogeneity across the eligible studies ($P$-values ≤ .05 and $I^2$-values ≥ 50% indicated heterogeneity for the $Q$ statistic).

Meta-regression analyses were conducted on the basis of age, publication year, country, sample type, and case number. We used Deeks' asymmetry test to evaluate potential publication bias and Fagan nomogram to evaluate the pretest probability and posttest probability of PLR and NLR. All tests were 2-sided, and a $P$-value < .05 was considered statistically significant.

3. Results

3.1. Literature search

The results of the selection process are shown in Figure 1. The initial search in the electronic databases yielded 116 relevant studies using the search strategy described above, of which 37 studies were excluded due to duplication. Additionally, 50 studies were excluded because they were letters, reviews, comments, animals, or cell line studies or had incomplete clinical data. After careful examination, 22 additional studies were excluded because they had index details missing or were not case-control studies. Finally, a total of 7 studies were included in the present meta-analysis.

3.2. Study characteristics

The features of the enrolled studies are listed in Table 1. The 7 studies were published between 2010 and 2018, and included 279 PCa patients and 135 controls. Four studies were conducted in Europe, and 3 studies were conducted in Asia. The quality assessment results of the included studies are shown in Figure 2. The results show that the included studies have high quality and can be used for meta-analysis.

3.3. Meta-analysis

The summary results for sensitivity, specificity, PLR and NLR are presented in Figure 3. The pooled sensitivity and specificity, PLR and NLR are presented in Figure 3. The pooled sensitivity
was 0.70 (95% CI 0.64–0.75), the specificity was 0.73 (95% CI 0.64–0.80), the PLR was 2.88 (95% CI 1.40–5.93), and the NLR was 0.38 (95% CI 0.20–0.71). Further, we noted that the pooled DOR of miR-141 for PCa was 9.94 (95% CI: 2.55–38.80) (Fig. 4). Finally, the summary area under the ROC curve was 0.83 (95% CI: 0.79–0.86) (Fig. 5).

3.4. Heterogeneity analysis
The pooled DOR was 9.94, with significant heterogeneity ($I^2=82.1\%$, $P\leq .05$), and meta-regression was conducted based on patient age, year of publication, country, sample type, and case number. The results suggested that heterogeneity was mainly derived from patient age (Fig. 6 and Table 2).

3.5. Clinical diagnostic efficiency
The analysis of Fagan nomogram was used to evaluate the changes in the pretest probability and the posttest probability in the diagnosis of PCa with miR-141. The pretest probability of PLR was 20%, and the posttest probability was 48%. The pretest probability of NLR was 20%, and the posttest probability decreased to 8% (Fig. 7).

3.6. Publication bias
We used Deeks’ funnel plot asymmetry test to evaluate publication bias. The funnel plots of the studies were symmetrical, and the results of the test showed no evidence of publication bias ($P = .56$) (Fig. 8).

4. Discussion
In 2019, the estimated number of new cases of PCa was 174,650, accounting for 20% of all cases in men. The early screening of PCa can aid in the early diagnosis and treatment of the disease, ultimately benefitting patients. The serum prostate-specific antigen test combined with digital rectal examination is a widely recognized screening method for PCa. Despite their widespread use, these tests have some limitations and drawbacks in the diagnosis of PCa. Compared with the traditional detection method, microRNAs have shown better sensitivity and specificity in the diagnosis of PCa. In particular, miR-141 is considered to be the most effective biological marker of PCa, wherein its expression level is 46 times higher than that of the normal control group.

This meta-analysis evaluated the diagnostic value of miR-141 for PCa and included 7 studies involving a total of 414 patients. The results show that the pooled sensitivity and specificity were 0.70 and 0.73, respectively. The missed diagnosis rate was 0.30
Figure 6. Meta-regression analyses for DOR. DOR = diagnostic odds ratio.

Table 2
Meta-regression.

| Variable | Coefficient | Std. Err. | P-value | RDOR | (95% CI) |
|----------|-------------|-----------|---------|------|----------|
| Case     | -0.03       | 0.03      | .25     | 0.97 | (0.90; 1.04) |
| Age      | 1.94        | 1.41      | .01     | 6.96 | (0.14; 344.15) |
| Year     | -1.98       | 1.56      | .07     | 0.14 | (0.00; 10.54) |
| Country  | 0.52        | 0.12      | .24     | 1.68 | (1.21; 2.34)  |
| Sample   | -0.81       | 1.13      | .51     | 0.44 | (0.02; 10.34) |

CI = confidence interval, RDOR = relative diagnostic odds ratio.
and 0.27, respectively, which showed that the diagnostic efficiency was high. In this study, the pooled PLR and NLR of miR-141 for PCa were 2.88 and 0.38, respectively, and the results showed an acceptable detection rate. These results suggest that the overall accuracy of PCa detection by miR-141 is relatively good. Next, the pooled DOR was 9.94, and the results suggested that miR-141 has outstanding discrimination ability for PCa. Furthermore, the AUC of the sROC curve was used to evaluate the overall diagnostic efficiency. The summary area under the ROC curve was 0.83, and the results indicated a high diagnostic value.

The $I^2$ value of the heterogeneity test of DOR was 82.1%, which indicated high heterogeneity. Therefore, meta-regression analysis was used to explore the possible sources of heterogeneity. The $P$-value of age was .01 ($<.05$), and the remaining $P$-values were all $>.05$. The result suggested that the age of patients is the main source of heterogeneity. Deeks’ funnel plot asymmetry test showed no evidence of publication bias ($P=.56$).

The results of the Fagan nomogram showed that it was increased significantly by testing miR-141 for diagnosing PCa. Upregulated miR-141 is suspicious for lung cancer, increasing the pretest probability of the PLR from 20% to the posttest probability of 48%. Furthermore, upregulated miR-141 decreased the pretest probability from 20% to 8%. Since miRNAs were first identified in 1993, many studies have examined whether the expression of certain miRNAs in PCa is associated with tumor risk and progression.$^{[31]}$ Based on the results of the current meta-analysis, we believe that the detection of miR-141 combined with conventional methods can help doctors treat and monitor disease progression. The detection of miR-141 is helpful for the diagnosis and treatment of PCa.
5. Conclusions
This meta-analysis suggests that miR-141 has a high diagnostic value for PCa. In the future, large-scale prospective studies are needed to verify and evaluate this result.

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References
[1] Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
[3] Wang Y, Guo J, Xu L, et al. Should bone scan be performed in Chinese prostate cancer patients at the time of diagnosis? Urol Int 2013;91:160–4.
[4] Obort AS, Ajadi MB, Akinfloye O. Prostate-specific antigen: any successor in sight? Rev Urol 2013;15:97–107.
[5] Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. Nat Rev Genet 2010;11:597–610.
[6] Chen M, Calin GA, Meng QH. Circulating microRNAs as promising tumor biomarkers. Adv Clin Chem 2014;67:189–214.
[7] Peng J, Xie Z, Cheng L, et al. Paired design study by real-time PCR: miR-378* and miR-145 are potent early diagnostic biomarkers of human colorectal cancer. BMC Cancer 2015;15:158.
[8] Lu J, Getz G, Miska EA, et al. MicroRNA expression profiles classify human cancers. Nature 2005;435:834–8.
[9] Mishra S, Deng JJ, Gowda PS, et al. Androgen receptor and microRNA-21 axis downregulates transforming growth factor beta receptor II (TGFBRII) expression in prostate cancer. Oncogene 2014;33:4097–106.
[10] Ghorbaniamehr N, Gharbi S, Korsching E, et al. miR-21-3p, miR-141-3p, and miR-205-5p levels in urine-promise biomarkers for the identification of prostate and bladder cancer. Prostate 2019;79:88–95.
[11] Song CJ, Chen H, Chen LZ, et al. The potential of microRNAs as human prostate cancer biomarkers: a meta-analysis of related studies. J Cell Biochem 2018;119:2763–86.
[12] Moher D, Liberati A, Tetzlaff J, et al. PRISMA GroupPreferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[13] Whiting PF, Weswood ME, Rutjes AW, et al. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC Med Res Methodol 2006;6:9.
[14] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[15] Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med 2002;21:1237–56.
[16] Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012;31:3805–20.
[17] Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219.
[18] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.
[19] Akobeng AK. Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. Acta Paediatr 2007;96:487–91.
[20] Porzyczki P, Ciszkowicz E, Semik M, et al. Combination of three microRNA (miR-141, miR-21, and miR-375) as potential diagnostic tool for prostate cancer recognition. Int Urol Nephrol 2018;50:1619–26.
[21] Kachakova D, Mitkova A, Popov E, et al. Combinations of serum prostate-specific antigen and plasma expression levels of let-7c, miR-30c, miR-141, and miR-375 as potential better diagnostic biomarkers for prostate cancer. DNA Cell Biol 2015;34:189–200.
[22] Haldrup C, Kosaka N, Ochiya T, et al. Profiling of circulating microRNAs for prostate cancer biomarker discovery. Drug Deliv Transl Res 2014;4:19–30.
[23] Kelly BD, Miller N, Sweeney KJ, et al. A circulating microRNA signature as a biomarker for prostate cancer in a high risk group. J Clin Med 2015;4:1369.
[24] Li Z, Ma YY, Wang J, et al. Exosomal microRNA-141 is upregulated in the serum of prostate cancer patients. Oncotargets Ther 2015;8:139–48.
[25] Yaman Agaoglu F, Kovancilar M, Dizdar Y, et al. Investigation of miR-21, miR-141, and miR-221 in blood circulation of patients with prostate cancer. Tumour Biol 2011;32:583–8.
[26] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
[27] Lima AR, Pinto J, Azevedo AI, et al. Identification of a biomarker panel for improvement of prostate cancer diagnosis by volatile metabolic profiling of urine. Br J Cancer 2019;121:837–68.
[28] Szeliski K, Adamowicz J, Gastecka A, et al. Modern urology perspectives on prostate cancer biomarkers. Cent European J Urol 2018;71:420–6.
[29] Yin C, Fang C, Weng H, et al. Circulating microRNAs as novel biomarkers in the diagnosis of prostate cancer: a systematic review and meta-analysis. Int Urol Nephrol 2016;48:1087–95.
[30] Mitchell PS, Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A 2008;105:10513–8.
[31] Shi XR, Xue L, Yang J, et al. An androgen-regulated miRNA suppresses Bak1 expression and induces androgen-independent growth of prostate cancer cells. Proc Natl Acad Sci U S A 2007;104:19983–8.