ORIGINAL ARTICLE

Prostate Cancer

The *PCA*3 test for guiding repeat biopsy of prostate cancer and its cut-off score: a systematic review and meta-analysis

Yong Luo, Xin Gou, Peng Huang, Chan Mou

The specificity of prostate-specific antigen (PSA) for early intervention in repeat biopsy is unsatisfactory. Prostate cancer antigen 3 (*PCA*3) may be more accurate in outcome prediction than other methods for the early detection of prostate cancer (PCa). However, the results were inconsistent in repeated biopsies. Therefore, we performed a systematic review and meta-analysis to evaluate the role of *PCA*3 in outcome prediction. A systematic bibliographic search was conducted for articles published before April 2013, using PubMed, Medline, Web of Science, Embase and other databases from health technology assessment agencies. The quality of the studies was assessed on the basis of QUADAS criteria. Eleven studies of diagnostic tests with moderate to high quality were selected. A meta-analysis was carried out to synthesize the results. The results of the meta-analyses were heterogeneous among studies. We performed a subgroup analysis (with or without inclusion of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP)). Using a *PCA*3 cutoff of 20 or 35, in the two sub-groups, the global sensitivity values were 0.93 or 0.80 and 0.79 or 0.75, specificities were 0.65 or 0.44 and 0.78 or 0.70, positive likelihood ratios were 1.86 or 1.58 and 2.49 or 1.78, negative likelihood ratios were 0.81 or 0.43 and 0.91 or 0.82 and diagnostic odd ratios (ORs) were 5.73 or 3.45 and 7.13 or 4.11, respectively. The areas under the curve (AUCs) of the summary receiver operating characteristic curve were 0.85 or 0.72 and 0.81 or 0.69, respectively. *PCA*3 can be used for repeat biopsy of the prostate to improve accuracy of PCa detection. Unnecessary biopsies can be avoided by using a PCa cutoff score of 20.
Asian Journal of Andrology (2014) 16, 487–492; doi: 10.4103/1008-682X.125390; published online: 28 March 2014

Keywords: meta-analysis; *PCA*3; prostate cancer; repeat biopsy; systematic review

INTRODUCTION

Prostate cancer (PCa) is recognized as one of the most common cancers in men in the Western world.[1] Early detection of PCa relies primarily on an elevated prostate-specific antigen (PSA) level and an abnormal digital rectal examination, which signal the need for prostate biopsy. However, 75% of men with PSA values between 2.5 and 10 ng ml^{-1} and/or a suspicious digital rectal examination have a negative first biopsy, even though 10%–35% of these men are diagnosed with PCa upon repeat biopsies.[2,3] The European Association of Urology guidelines recommend a repeat biopsy in men who have a negative first biopsy, but a persistent suspicion of PCa.[4] However, the repeat biopsies are negative in 80% of examined men. Discomfort, anxiety and severe complications can be associated with prostate biopsies. Repeated biopsies also result in a greater economic cost.[2,3] To avoid unnecessary biopsies and increase the probability of detecting PCa during a repeat biopsy, additional tests are needed. In this regard, the prostate cancer antigen 3 (*PCA*3) assay, a new PCa gene-based marker, appears to be promising. *PCA*3 expression has been found to be 66-fold higher than that in benign and normal prostate tissue in > 95% of malignant prostate tissue tested.[5–7] Numerous studies have shown a high level of *PCA*3 during the first biopsy. The sensitivity and specificity have been

reported to be as high as 82.3% and 89.0%, respectively, with small differences.[8–11] However, these results differed in repeated biopsies. To clarify the discrepancy, we performed a meta-analysis.

MATERIALS AND METHODS

Data collection

A systematic bibliographic search was conducted for articles published before April 2013, using PubMed, Medline, Web of Science, Embase and databases from health technology assessment agencies. Additionally, manual searches were performed in journals specializing in cancer and urology. The search strategy consisted of consecutively entering the following key words: "prostate"; "prostatic neoplasms"; "prostate" and "cancer"; "carcinoma" or "tumour"; "PCa"; "upm3"; "dd3"; "pca3"; "prostate cancer antigen3" and "aptimapca3". Abstracts or unpublished reports were not included. No language restrictions were applied. All non-English articles were translated if necessary.

The inclusion criteria included studies whose population consisted of adult men who had undergone a repeat biopsy for PCa. The intervention must have consisted of a quantitative determination of *PCA*3 gene expression in urine samples by molecular biology methods. The prostate biopsy was the gold

standard with which to assess the technique. The results had to include the specific values of the diagnostic tests, such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and receiver operating characteristic (ROC) curves, which must have been calculated using true positives, false positives, false negatives and true negatives. We also collected the following characteristics: the name of the first author of the study, the year of publication, the population studied, the mean age of the subjects, the mean PSA level and the cutoff point. The bibliographic references were selected individually by two researchers. All references were full articles. Quality assessment was based on the QUADAS questionnaire.

Statistical analysis of the included studies

The data from each study were organized systematically and extracted to obtain the true positives, false positives, false negatives, and true negatives. Meta-DiSc software was used to calculate the indices of diagnostic validity, including the sensitivity, specificity, PPV, NPV, likelihood ratio negative, likelihood ratio positive and diagnostic odds ratio (OR). This allowed us to assess the discriminative power of the *PCA*3 test. Each value was determined together with a 95% confidence interval.

We conducted the meta-analysis in accordance with evidence-based data we extracted. We evaluated the quality of the articles according to the QUADAS questionnaire. Meta-DiSc software (version 1.4) was used to aggregate the results. First, we determined the possible existence of a threshold effect by calculating the Spearman's correlation coefficient and by using a graphic representation of "sensitivity" or "1-specificity" on an ROC space. Second, the possible heterogeneity of the studies was assessed by a chi-square test for sensitivity, specificity, PPV and NPV. The Q value was used to determine the probability coefficients and the OR. The results were represented in a forest plot. If there was evidence of a threshold effect, the studies were combined to create a summarized receiver operating characteristic, and the area under the curve (AUC) was calculated. The analysis was performed following the random effects model, as well as subgroup analysis if heterogeneity was found.

RESULTS

Descriptive analysis of the included studies

The systematic search for original articles yielded 900 bibliographic references. After reading the full text of all articles, 11 studies on repeat biopsy were included (**Figure 1**).[12–22] All studies had adequate sensitivity, specificity, PPV and NPV. According to the QUADAS questionnaire (**Table 1**), the quality of the studies on diagnostic testing was moderate to high.
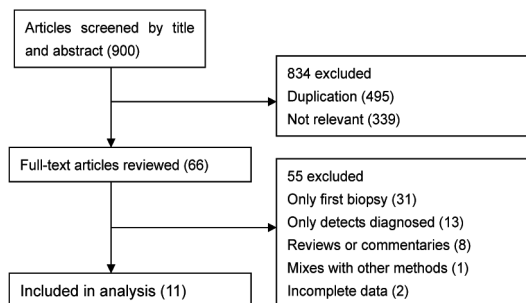

Figure 1: General outline for the selection of the studies included.

The studies retrieved data from a total of 3373 patients with a mean age between 62.5 and 67.0 years and mean PSA levels ranging from 4.8 to 16.0 ng ml^{-1} (**Table 2**). All patients underwent a repeat biopsy for comparison with the antigen determination. The intervention consisted of a quantitative determination of the *PCA*3 gene in urine samples of the patients. The studies presented the results as sensitivity, specificity, PPV, NPV and ROC curves (**Tables 3** and **4**). Using a *PCA*3 cutoff of 20 or 35, the sensitivities were between 67.0% and 92.0% or 38.0% and 78.6%,

Table 1: The QUADAS questionnaire evaluation of the quality of the 11 articles

Reference	Selection	Interval	GS	New test	Blinded	Same data	Interpretation	Losses explanation
Pepe and Aragona, 2013[12]	Yes	No	Yes	Yes	No	Yes	Yes	No
Goode *et al.*, 2013[13]	Yes	n.d.	Yes	Yes	n.d.	Yes	Yes	No
Wu *et al.*, 2012[14]	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Pepe *et al.*, 2012[15]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Bollito *et al.*, 2012[16]	Yes	No	Yes	Yes	No	Yes	Yes	No
Barbera *et al.*, 2012[17]	Yes	No	Yes	Yes	No	Yes	Yes	No
Auprich *et al.*, 2012[18]	Yes	No	Yes	Yes	n.d.	Yes	Yes	No
Pepe and Aragona, 2011[19]	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Remzi *et al.*, 2010[20]	Yes	No	Yes	Yes	No	Yes	Yes	No
Aubin *et al.*, 2010[21]	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Haese *et al.*, 2008[22]	Yes	No	Yes	Yes	No	Yes	Yes	Yes

GS: gold standard; n.d.: not described

Table 2: Main characteristics of the 11 included studies

Reference	Population	Mean age	Mean PSA	Sample
Pepe and Aragona, 2013[12]	100	66.0	7.9	Urine
Goode *et al.*, 2013[13]	167	66.0	4.8	Urine
Wu *et al.*, 2012[14]	103	63.5	11.0	Urine
Pepe *et al.*, 2012[15]	118	62.5	8.5	Urine
Bollito *et al.*, 2012[16]	509	67.0	6.7	Urine
Barbera *et al.*, 2012[17]	177	64.0	9.5	Urine
Auprich *et al.*, 2012[18]	127	63.0	16.0	Urine
Pepe and Aragona, 2011[19]	74	64.0	8.9	Urine
Remzi *et al.*, 2010[20]	463	64.9	7.2	Urine
Aubin *et al.*, 2010[21]	1072	n.d.	n.d.	Urine
Haese *et al.*, 2008[22]	463	65.0	7.0	Urine

n.d.: not described; PSA: prostate-specific antigen

Table 3: Diagnostic results based on the data retrieved from the articles included (score 20)

References	TP	FP	FN	TN	S	E	PPV	NPV
Pepe and Aragona, 2013[12]	26	60	2	12	92.9	16.7	30.2	85.7
Wu *et al.*, 2012[14]	24	23	13	43	67.0	64.0	52.0	78.0
Pepe *et al.*, 2012[15]	29	62	3	24	90.6	27.9	31.9	88.9
Bollito *et al.*, 2012[16]	108	215	15	171	88.2	44.3	40.7	89.6
Barbera *et al.*, 2012[17]	44	96	4	33	91.7	25.6	31.5	89.5
Auprich *et al.*, 2012[18]	35	62	9	21	85.0	25.3	38.0	77.8
Pepe and Aragona, 2011[19]	25	33	2	14	92.6	21.6	43.1	88.9
Remzi *et al.*, 2010[20]	94	165	34	170	73.4	50.7	36.3	83.3
Aubin *et al.*, 2010[21]	134	380	56	502	70.5	56.9	26.1	89.9
Haese *et al.*, 2008[22]	94	165	34	170	73.4	50.7	36.3	83.3

E: specificity; FN: false negatives; FP: false positives; NPV: negative predictive value; PPV: positive predictive value; S: sensitivity; TN: true negatives; TP: true positives

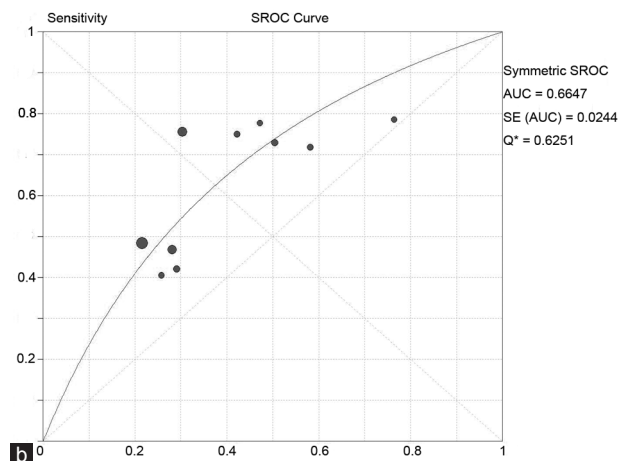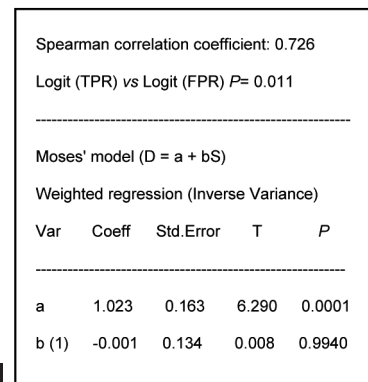**Table 4: Diagnostic results based on the data retrieved from the articles included (score 35)**

References	TP	FP	FN	TN	S	E	PPV	NPV
Pepe and Aragona, 2013[12]	22	55	6	17	78.6	23.6	28.6	73.9
Goode *et al.*, 2013[13]	8	43	11	105	42.0	71.0	15.7	90.5
Wu *et al.*, 2012[14]	15	17	22	49	38.0	77.0	50.0	66.0
Pepe *et al.*, 2012[15]	23	50	9	36	71.9	41.8	31.5	80.0
Bollito *et al.*, 2012[16]	93	117	30	269	75.2	69.8	52.0	86.7
Barbera *et al.*, 2012[17]	35	65	13	64	73.0	41.8	35.0	80.6
Auprich *et al.*, 2012[18]	33	35	11	48	75.0	57.8	48.5	81.4
Pepe and Aragona, 2011[19]	21	25	6	28	70.4	43.5	42.2	71.5
Remzi *et al.*, 2010[20]	60	94	68	241	46.9	71.9	38.9	77.9
Aubin *et al.*, 2010[21]	92	190	98	692	48.4	78.6	32.6	87.6
Haese *et al.*, 2008[22]	60	94	68	241	47.0	72.0	39.0	78.0

E: specificity; FN: false negatives; FP: false positives; NPV: negative predictive value; PPV: positive predictive value; S: sensitivity; TN: true negatives; TP: true positives

Figure 2: (**a**) Analysis of the threshold effect: Spearman's correlation coefficient. (**b**) Analysis of the threshold effect: ROC space. ROC: receiver operating characteristic.

respectively; whereas, the specificities were between 16.7% and 64.0% or 23.6% and 78.6%, respectively; the PPV and NPV values ranged from 26.1% to 52.0% or 15.7% to 52.0% and from 77.8% to 89.9% or 66.0% to 90.5%, respectively and the AUCs were between 0.577 and 0.730 or 0.605 and 0.715, respectively. All studies reported 95% confidence intervals. Cutoff points were established based on *PCA*3 scores. We divided the 11 studies into two groups: group A included high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP); whereas, group B did not.[13,14,18,20–22]

Meta-analysis

The analysis was conducted using the 11 articles above. With a *PCA*3 cutoff of 20 or 35, Spearman's correlation coefficient was 0.841 ($P = 0.002$) and 0.726 ($P = 0.011$), respectively, and the ROC space showed a curvilinear trend. The results suggest the existence of a threshold effect (**Figure 2a** and **2b**). Group A, which contained subjects with HGPIN and ASAP, was not similar to Group B. We then performed a separate meta-analysis on each group. The pooled sensitivities of using a *PCA*3 cutoff of 20 or 35 in group A and group B were 72% or 49% and 90% or 75%, respectively (**Figure 3a–3d**), and the specificities were 53% or 35% and 74% or 57%, respectively (**Figure 3e–3h**). Using a *PCA*3 cutoff of 20, the positive likelihood ratio (LR), negative LR and diagnostic OR; the AUCs were 1.37, 0.49, 3.18 and 0.8462, respectively (**Figure 4a–4d**).

DISCUSSION

In this review, we analyzed the available literature regarding the use of urine *PCA*3 as a guiding marker for repeat prostate biopsy for detecting PCa. Although the levels of *PCA*3 in the urine are lower than in the prostate tissue, *PCA*3 is readily detectable in urine samples. Clearly, *PCA*3 in the first biopsy shows excellent value. Some studies showed that during the first biopsy, when a *PCA*3 cutoff score of 35 was used, the sensitivity and specificity were up to 82.3% and 89.0%, respectively, with little differences between these studies. The results were much better than those using PSA. The best PSA cutoff value showed only 57.4% and 53.8% sensitivity and specificity, respectively.[10–13,23–25] In an American study, the diagnostic accuracy of the score was evaluated in men undergoing an initial biopsy (277) and a repeat biopsy (280).[26] In an European study, the AUC of *PCA*3 was 0.761 in the initial biopsy and 0.658 in the repeat biopsy.[22] This finding suggests that *PCA*3 is more accurate than PSA at guiding both repeat biopsy and initial biopsy. The diagnostic accuracy was not affected by prostate volume, age or total PSA ranges.[22,26]

For repeat biopsy cases, there was some variability among the studies in terms of *PCA*3. *PCA*3 has great value as a diagnostic tool. However, the problem is the optimal cutoff value. Although the specificity of a score of 20 is lower than that of 35, the values of other parameters are superior at a score of 20 than at a score of 35. The sensitivity results indicate that 75% of patients can be diagnosed by assessing *PCA*3 and using a cutoff score of 20. Thus, the results suggest that 20 is an appropriate cutoff score. The negative LR results
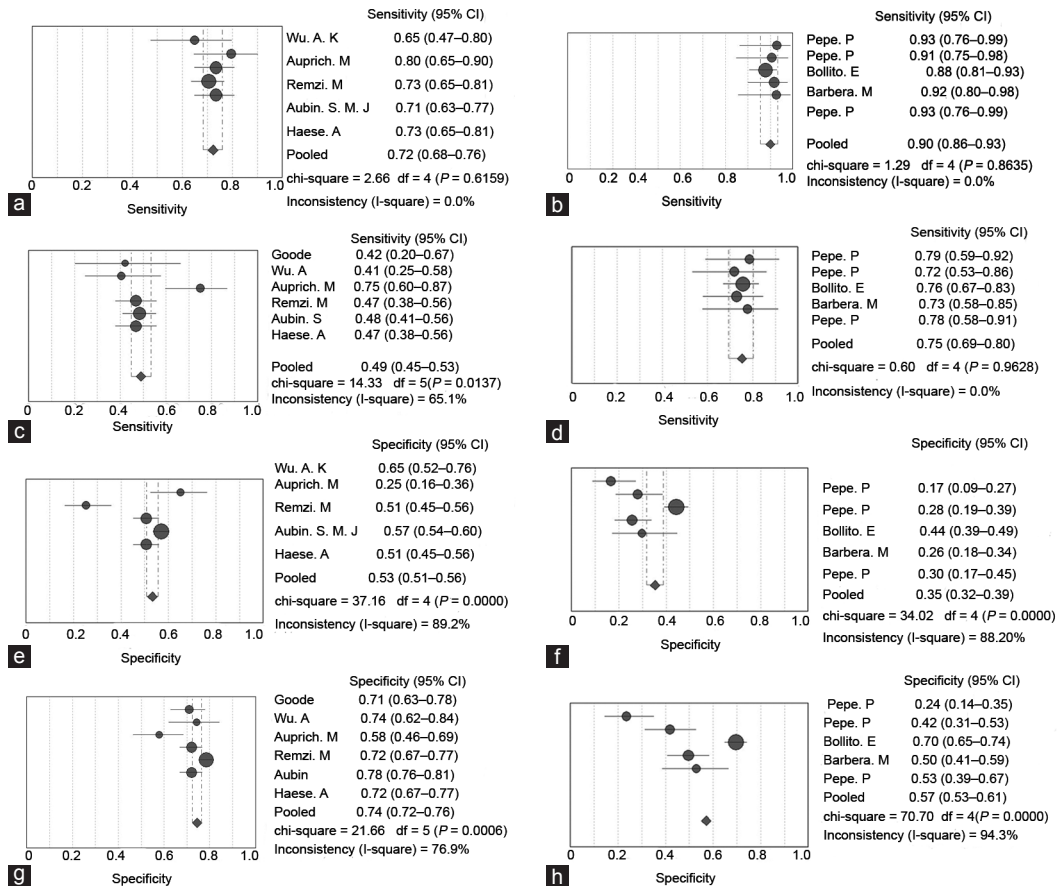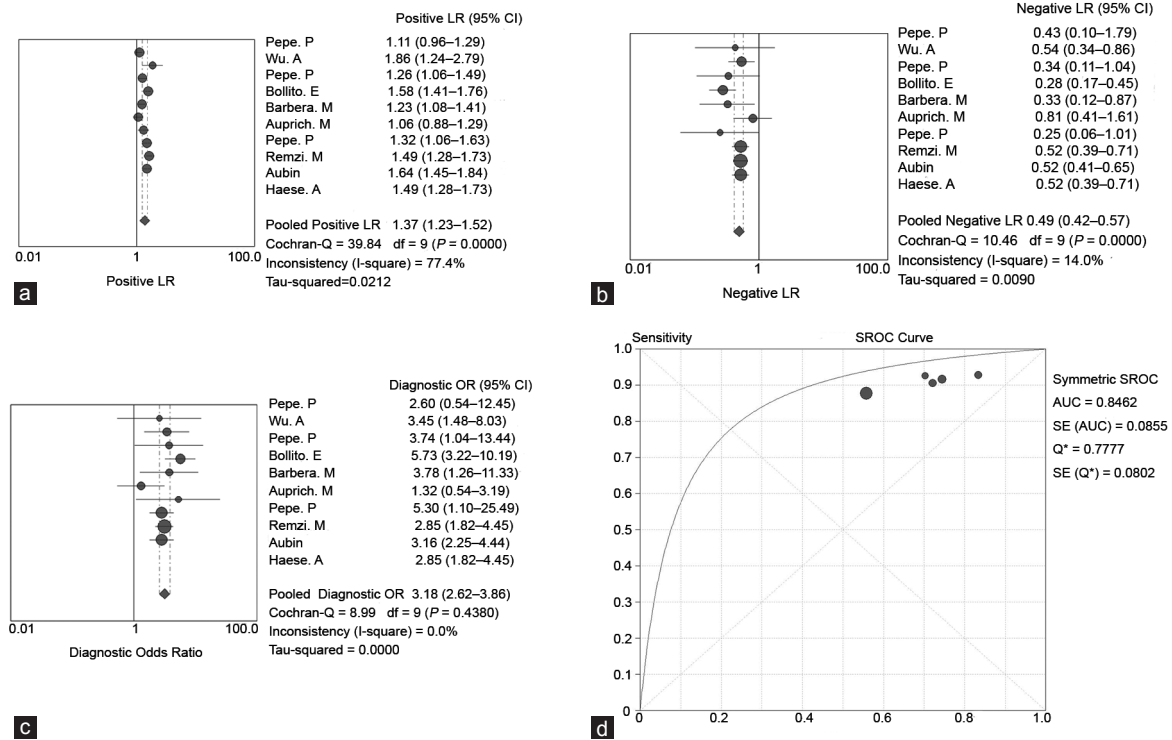
Figure 3: (**a**) Forest plots of the meta-analysis values for: sensitivity (score 20 group a). (**b**) Forest plots of the meta-analysis values for: sensitivity (score 20 group b). (**c**) Forest plots of the meta-analysis values for: sensitivity (score 35 group a). (**d**) Forest plots of the meta-analysis values for: sensitivity (score 35 group b). (**e**) Forest plots of the meta-analysis values for: specificity (score 20 group a). (**f**) Forest plots of the meta-analysis values for: specificity (score 20 group b). (**g**) Forest plots of the meta-analysis values for: specificity (score 35 group a). (**h**) Forest plots of the meta-analysis values for: specificity (score 35 group b).

indicate that *PCA*3 detection will lead to a significant reduction in unnecessary biopsies, by more than half. The positive LR results indicate that the probability of a patient with positive *PCA*3 is almost 1.5 times higher than that of a patient with negative *PCA*3 to have PCa. The AUC can be interpreted as the performance acceptability of the diagnostic test. The AUC of a score of 20 is higher than that of a score of 35, which indicates greater diagnostic value. According to the analyzed data and the meta-analysis, a *PCA*3 score cutoff of 20 is better than a score cutoff of 35. Although there were differences in these studies, the *PCA*3 results indicate that the detection of this biomarker has acceptable diagnostic validity indices and adequate sensitivity and can be used for guiding repeat biopsies of the prostate for PCa testing.

Using a *PCA*3 score cutoff of 20, group A showed better results than group B. Although group A had a slightly lower sensitivity than that of group B (72% *vs* 90%), the specificity of group A was higher (53% *vs* 35%). The specificity of group B was too low for diagnosis. Group A had more balanced sensitivity and specificity values, possibly because group A subjects had a higher *PCA*3 score. Most patients were still diagnosed with HGPIN and ASAP on repeat biopsy. Some studies showed that subjects diagnosed with HGPIN and ASAP had higher scores than healthy controls.[25] Further studies are needed to determine why HGPIN and ASAP higher than normal. On a repeat biopsy, a *PCA*3

cut-off score of 20 with HGPIN and ASAP is a valuable diagnostic tool and can be clinically applied.

There are several limitations of our meta-analysis. Some studies were not performed blinded; whereas, some lacked explanation of the loss of the patients. But most have given explanations. These do not affect the results. We have tried to avoid these biases by expanding our search to several databases and conducting a rigorous screening for articles. We evaluated the quality of the articles according to the QUADAS questionnaire evaluation. The quality of the studies on diagnostic testing was moderate to high. We eliminated poor quality papers and avoided language restrictions. However, there were potential publication biases, such as unpublished studies and reports from commercial enterprises, which were excluded. It should be noted that the *PCA*3 score is inconclusive. Some studies used a cutoff score of 25, but most of the studies that we searched used a cutoff score of 20. Moreover, several studies showed that cut-off scores of 20 and 25 yielded similar results.[25,26] Whereas, other genes and proteins such as AMACR, HPG-1, STAMP1, STAMP2, DPIV, Trp-p8, GSTM1, GSTT1, CYP1A1, CYP1A2, CYP2E1, MDM2 T309G and NPY[27-36] have also been considered as prostate-specific markers and their expression is altered in pathologic conditions, *PCA*3 is the only gene with that can be used with high specificity as a diagnostic tool.[37] Additionally, *PCA*3 detection is a minimally invasive test. Furthermore, *PCA*3 detection

Figure 4: (**a**) Forest plots of the meta-analysis values for: positive likelihood ratio (score 20). (**b**) Forest plots of the meta-analysis values for: negative likelihood ratio. (**c**) Forest plot of the meta-analysis values for: diagnostic odds ratio. (**d**) Forest plot of the meta-analysis values for: SROC curve (score 20 group a).

has good diagnostic performance because the sample is collected by urinary sediment after prostate massage.[38]

Taking the above findings together, early use of the noninvasive method of *PCA*3 detection may lead to a significant reduction in the number of repeat biopsies that is conducted. Several studies showed that the *PCA*3 score was closely linked to the Gleason score and clinical stage. However, some studies showed conflicting result and questioned the relationship between the *PCA*3 score and PCa aggressiveness.[27,39] The *PCA*3 score decrease in patients who had been diagnosed with PCa, but was still higher than normal.[13,18-20,22] This finding does not affect the value of *PCA*3 as a diagnostic tool. Whether *PCA*3 can be used for clinical staging is not conclusive, and the association between *PCA*3 score and Gleason score requires further evaluation in controlled studies. Based on the results, we conclude that a *PCA*3 cutoff score of 20 is better than a cutoff score of 35 and that *PCA*3 is a much better diagnostic marker than PSA. This finding will be clinically useful for improving diagnostic accuracy and avoiding unnecessary biopsies in patients. However, more studies are needed to determine the costs and efficacy of this approach.

AUTHOR CONTRIBUTIONS

YL and XG conceived and designed the experiments. YL and PH extracted and analyzed the data. YL and CM checked the data. YL and XG drafted the paper.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

1   Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62: 10–29.
2   Matlaga BR, Eskew LA, McCullough DL. Prostate biopsy: indications and technique. *J Urol* 2003; 169: 12–9.
3   Raja J, Ramachandran N, Munneke G, Patel U. Current status of transrectal ultrasound-guided prostate biopsy in the diagnosis of prostate cancer. *Clin Radiol* 2006; 61: 142–53.
4   Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, *et al.* European Association of Urology. EAU guidelines on prostate cancer. *Eur Urol* 2008; 53: 68–80.
5   Bussemakers MJ, van Bokhoven A, Verhaegh GW, Smit FP, Karthaus HF, *et al.* DD3: a new prostate-specific gene, highly overexpressed in prostate cancer. *Cancer Res* 1999; 59: 5975–9.
6   Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ, *et al.* DD3PCA3-based molecular urine analysis for the diagnosis of prostate cancer. *Eur Urol* 2003; 44: 8–15.
7   Schalken J. Interview with Jack Schalken: PCA3 and its use as a diagnostic test in prostate cancer. Interview by Christine McKillop. *Eur Urol* 2006; 50: 153–4.
8   Crawford ED, Rove KO, Trabulsi EJ, Qian JQ, Drewnowska KP, *et al.* Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1, 962 Cases. *J Urol* 2012; 188: 1726–31.
9   Ng CF, Yeung R, Chiu PK, Lam NY, Chow J, *et al.* The role of urine prostate cancer antigen 3 mRNA levels in the diagnosis of prostate cancer among Hong Kong Chinese patients. *Hong Kong Med J* 2012; 18: 459–65.
10   Ochiai A, Okihara K, Kamoi K, Oikawa T, Shimazui T, *et al.* Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy. *BJU Int* 2013; 111: 928–33.
11   Salagierski M, Mulders P, Schalken JA. Predicting prostate biopsy outcome using a PCA3-based nomogram in a polish cohort. *Anticancer Res* 2013; 33: 553–8.
12   Pepe P, Aragona F. Prostate cancer detection rate at repeat saturation biopsy: PCPT risk calculator versus PCA3 score versus case-finding protocol. *Can J Urol* 2013; 20: 6620–4.
13   Goode RR, Marshall SJ, Duff M, Chevli E, Chevli KK. Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients. *Prostate* 2013; 73: 48–53.
14   Wu AK, Reese AC, Cooperberg MR, Sadetsky N, Shinohara K. Utility of PCA3 in patients undergoing repeat biopsy for prostate cancer. *Prostate Cancer Prostatic Dis* 2012; 15: 100–5.
15   Pepe P, Fraggetta F, Galia A, Skonieczny G, Aragona F. PCA3 score and prostate cancer diagnosis at repeated saturation biopsy. Which cut-off: 20 or 35? *Int Braz J Urol* 2012; 38: 489–95.
16   Bollito E, De Luca S, Cicilano M, Passera R, Grande S, *et al.* Prostate cancer gene

3 urine assay cutoff in diagnosis of prostate cancer: a validation study on an Italian patient population undergoing first and repeat biopsy. *Anal Quant Cytol Histol* 2012; 34: 96–104.

17 Barbera M, Pepe P, Paola Q, Aragona F. PCA3 score accuracy in diagnosing prostate cancer at repeat biopsy: our experience in 177 patients. *Arch Ital Urol Androl* 2012; 84: 227–9.

18 Auprich M, Augustin H, Budaus L, Kluth L, Mannweiler S, *et al*. A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen, prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second and third repeat prostate biopsy. *BJU Int* 2012; 109: 1627–35.

19 Pepe P, Aragona F. PCA3 score vs PSA free/total accuracy in prostate cancer diagnosis at repeat saturation biopsy. *Anticancer Res* 2011; 31: 4445–9.

20 Remzi M, Haese A, Van Poppel H, De la Taille A, Stenzl A, *et al*. Follow-up of men with an elevated PCA3 score and a negative biopsy: does an elevated PCA3 score indeed predict the presence of prostate cancer? *BJU Int* 2010; 106: 1138–42.

21 Aubin SMJ, Reid J, Sarno MJ, Blase A, Aussie J, *et al*. PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial. *J Urol* 2010; 184: 1947–52.

22 Haese A, de la Taille A, van Poppel H, Marberger M, Stenzl A, *et al*. Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. *Eur Urol* 2008; 54: 1081–8.

23 Fradet Y, Saad F, Aprikian A, Dessureault J, Elhilali M, *et al*. uPM3, a new molecular urine test for the detection of prostate cancer. *Urology* 2004; 64: 311–5.

24 Tinzl M, Marberger M, Horvath S, Chypre C. DD3^{PCA3} RNA analysis in urine: a new perspective for detecting prostate cancer. *Eur Urol* 2004; 46: 182–6.

25 Tombal B, Andriole GL, de la Taille A, Gontero P, Haese A, *et al*. Clinical judgment versus biomarker prostate cancer gene 3: which is best when determining the need for repeat prostate biopsy? *Urology* 2013; 81: 998–1004.

26 Deras IL, Aubin SM, Blase A, Day JR, Koo S, *et al*. PCA3: a molecular urine assay for predicting prostate biopsy outcome. *J Urol* 2008; 179:1587–92.

27 Murata M, Watanabe M, Yamanaka M, Kubota Y, Ito H, *et al*. Genetic polymorphisms in cytochrome P450 (CYP) 1A1, CYP1A2, CYP2E1, glutathione S-transferase (GST) M1 and GSTT1 and susceptibility to prostate cancer in the Japanese population. *Cancer Lett* 2001; 165: 171–7.

28 Tsavaler L, Shapero MH, Morkowski S, Laus R. Trp-p8, a novel prostate-specific gene, is up-regulated in prostate cancer and other malignancies and shares high homology with transient receptor potential calcium channel proteins. *Cancer Res* 2001; 61: 3760–9.

29 Korkmaz KS, Elbi C, Korkmaz CG, Loda M, Hager GL, *et al*. Molecular cloning and characterization of STAMP1, a highly prostate-specific six transmembrane protein that is overexpressed in prostate cancer. *J Biol Chem* 2002; 277: 36689–96.

30 Herness EA, Naz RK. A novel human prostate-specific gene-1 (HPG-1) molecular cloning, sequencing, and its potential involvement in prostate carcinogenesis. *Cancer Res* 2003; 63: 329–36.

31 Jiang Z, Wu CL, Woda BA, Iczkowski KA, Chu PG, *et al*. Alpha-methylacyl-CoA racemase: a multi-institutional study of a new prostate cancer marker. *Histopathology* 2004; 45: 218–25.

32 Korkmaz CG, Korkmaz KS, Kurys P, Elbi C, Wang L, *et al*. Molecular cloning and characterization of STAMP2, an androgen-regulated six transmembrane protein that is overexpressed in prostate cancer. *Oncogene* 2005; 24: 4934–45.

33 Ruscica M, Dozio E, Boghossian S, Bovo G, Martos Riaño V, *et al*. Activation of the Y1 receptor by neuropeptide Y regulates the growth of prostate cancer cells. *Endocrinology* 2006; 147: 1466–73.

34 Yang J, Gao W, Song NH, Wang W, Zhang JX, *et al*. The risks, degree of malignancy and clinical progression of prostate cancer associated with the MDM2 T309G polymorphism: a meta-analysis. *Asian J Androl* 2012; 14: 726–31.

35 Ribarska T, Bastian KM, Koch A, Schulz WA. Specific changes in the expression of imprinted genes in prostate cancer: implications for cancer progression and epigenetic regulation. *Asian J Androl* 2012; 14: 436–50.

36 Walia G, Sun Y, Soule HR. Global advances in prostate cancer diagnosis and therapy. *Asian J Androl* 2013; 15: 299–300.

37 Tricoli JV, Schoenfeldt M, Conley BA. Detection of prostate cancer and predicting progression: current and future diagnostic markers. *Clin Cancer Res* 2004; 10: 3943–53.

38 Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, *et al*. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem* 2006; 52: 1089–95.

39 Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, *et al*. PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. *Urology* 2007; 69: 532–5.