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ORIGINAL ARTICLE

Prostate Disease

The prognostic value of lymphovascular invasion in radical prostatectomy: a systematic review and meta-analysis

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To systematically evaluate the prognostic value of lymphovascular invasion (LVI) in radical prostatectomy (RP) by a meta-analysis based on the published literature. To identify relevant studies, PubMed, Cochrane Library, and Web of Science database were searched from 1966 to May 2014. Finally, 25 studies (9503 patients) were included. LVI was found in 12.2% (1156/9503) of the RP specimens. LVI was found to be correlated with higher pathological tumor stages (greater than pT3 stage) (risk ratio [RR] 1.90, 95% confidence interval [CI] 1.73–2.08, $P < 0.00001$), higher Gleason scores (greater than GS = 7) (RR 1.30, 95% CI 1.23–1.38, $P < 0.00001$), positive pathological node (pN) status (RR 5.67, 95% CI 3.14–10.24, $P < 0.00001$), extracapsular extension (RR 1.72, 95% CI 1.46–2.02, $P < 0.00001$), and seminal vesicle involvement (RR 3.36, 95% CI 2.41–4.70, $P < 0.00001$). The pooled hazard ratio (HR) was statistically significant for Biochemical Recurrence-Free (BCR-free) probability (HR 2.05, 95% CI 1.64–2.56; Z = 6.30, $P < 0.00001$). Sensitivity analysis showed that the pooled HR and 95% CI were not significantly altered by the omission of any single study. Begg's Funnel plots showed no significant publication bias ($P = 0.112$). In conclusion, LVI exhibited a detrimental effect on the BCR-Free probability and clinicopathological features in RP specimens, and may prove to be an independent prognostic factor of BCR.

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Keywords: lymphovascular invasion; meta-analysis; prognosis; prostate cancer; radical prostatectomy

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the sixth leading cause of cancer-related death in Caucasian men, and there were estimated 238 590 new PCa cases and 29 720 deaths from PCa in the United States in 2014.[1] With advances in the minimally invasive technologies, radical prostatectomy (RP) as the standard treatment has made great progress in improving perioperative outcomes. Nevertheless, early biochemical recurrence (BCR) occurred in approximately 20% patients undergoing RP,[2,3] in whom the 5-year metastasis rate was as high as 30%–44%.[4] Thus, it is imperative for clinicians to identify risk factors of post-RP BCR, and provide advisable indexes for adjuvant therapies including external beam radiotherapy (EBRT), intensity-modulated radiotherapy, and androgen deprivation therapy.

To date, although some potential biomarkers including Lymphovascular Invasion (LVI) have been added to the pathological reports of PCa patients who underwent prostatectomy, their impact on prognosis such as BCR has not been sufficiently evaluated.[5] LVI has been documented as a poor prognostic factor in many solid tumors.[6,7] Some authors have demonstrated an association between the presence of LVI in prostatectomy specimens and BCR. Although the College of American Pathologists (CAP) suggested that LVI should be reported in the routine examination of RP specimens in the 2010 consensus statement, there is a lack of convincing evidence to support its prognostic value.[8] Therefore, we conducted a systematic review of current publications to assess the prognostic value of LVI in BCR, and a meta-analysis was performed for the extracted data that could be merged.

MATERIALS AND METHODS

Literature search

We search Electronic databases including PubMed, Web of Science and the Cochrane Library for published studies that analyzed the prognostic value of LVI in PCa up to May 31, 2014. The following Medical Subject Headings terms and free texts were used: "lymphovascular," "microvascular," "vascular," "vessel," "invasion," "prostate," "prostatic," "cancer," "carcinoma," "neoplasm," "tumor," and "mass." The searching strategies and results are shown in **Table 1**. In addition, a full manual search from the reference list of each identified article was performed.

Study selection

We defined the inclusion and exclusion criteria at the initiation of the search. Studies were included when they met the following

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Table 1: Searching strategies and results

Database	*Date*	*Search strategy*	*Results*
PubMed	Up to May 2014	No. 1 – "Lymphovascular" OR "microvascular" OR "vascular" OR "vessel" (abstract/title) No. 2 – "Invasion" (abstract/title) No. 3 – "Prostate" OR "prostatic" (abstract/title) No. 4 – "Cancer" OR "carcinoma" OR "neoplasm" OR "tumor" OR "mass" (abstract/title) No. 5 – No. 1 and No. 2 and No. 3 and No. 4	313
Web of Science	Up to May 2014	No. 1 – "Lymphovascular" OR "microvascular*" OR "vascular" OR "vessel" (theme) No. 2 – "Invasion" (theme) No. 3 – "Prostate" OR "prostatic" (theme) No. 4 – "Cancer" OR "carcinoma" OR "neoplasm" OR "tumor" OR "mass" (theme) No. 5 – No. 1 and No. 2 and No. 3 and No. 4	721
Cochrane Library	Up to May 2014	No. 1 – "Lymphovascular" OR "microvascular" OR "vascular" OR "vessel" (abstract/title/key word) No. 2 – "Invasion" (abstract/title/key word) No. 3 – "Prostate" OR "prostatic" (abstract/title/key word) No. 4 – "Cancer" OR "carcinoma" OR "neoplasm" OR "tumor" OR "mass" (abstract/title/key word) No. 5 – No. 1 and No. 2 and No. 3 and No. 4	1

criteria: (1) studies that included definitive diagnosis of PCa; (2) studies that assessed LVI in RP specimens involving lymphatic or vascular invasion for which no attempt was made to differentiate them; (3) studies that chose RP as the only treatment; (4) studies that investigated the relationship between LVI and patient pathological outcomes or the correlation between LVI with preoperative prostate specific antigen (PSA) and pathological parameters; and (5) studies that offered a hazard ratio (HR) and 95% confidence interval (CI) directly or rendered the data that could be used to calculate HR and 95% CI. The exclusion criteria were: (1) review articles, letters to the editor, commentaries, or case reports; (2) studies that duplicated patient populations that had been reported in previous publications; and (3) studies on PCa cell lines or animal models. The whole process was monitored by two reviewers (YH and HH) independently. Discrepancies between the reviewers were resolved by a consensus meeting with three senior investigators (YG, YH, and XGC) who made the final decision regarding inclusion or exclusion of the study.

Data extraction

The following specified data were gathered from each eligible study: (1) main characteristics including the author, country, publication year, institution, recruitment period, study design, pathology stain method, definition of LVI, definition of BCR, the number of patients, median age at operation, the number of pelvic lymph node dissection (PLND), neoadjuvant (neo), androgen deprivation therapy (ADT), external beam radiotherapy (EBRT), and median follow-up time (**Supplementary Table 1**); (2) Tumor-Node-Metastasis (TNM) stage characteristics, Gleason score, and correlation between LVI and preoperative PSA and pathological parameters (**Supplementary Table 2**); (3) HR of LVI in univariate or multivariate Cox analyses, Co-factors, and the conclusion of each study concerning whether LVI was an independent predictor (**Supplementary Table 3**).

Statistical analysis

The primary objective of this review was to determine differences in survival outcomes between patients with negative LVI and positive LVI. HR and 95% CI were collected from each study if they were not directly reported, and the HR was estimated according to the method reported by Tierney *et al*.[9] The overall pooled HR was estimated by calculating the weighted average of the log-HRs and their 95% CI from each study. An observed HR >1 implied a poor survival outcome for patients with positive LVI. The impact of LVI on the outcome was considered as an independent predictor if the 95% CI did not overlap with 1 and $P < 0.05$. Subgroup analysis was performed to check whether the pooled HR was influenced by the region and number of patients, pathologic N stage, median follow-up, analysis results, definition of BCR, staining method, and staging system. In order to assess the stability of the combined HR, sensitivity analysis was performed by removing one study. The heterogeneity of the combined HR was evaluated using the Chi-square (χ^2 test) and inconsistency (I^2 test). Meta-analysis used the fixed-effect model,[10] when $P \geq 0.1$ and $I^2 \leq 50\%$, which indicated a moderate heterogeneity between studies,[11] whereas when $P < 0.1$ or $I^2 > 50\%$, which indicated large heterogeneity,[11] the random-effect model was applied.[12] In addition, publication bias was evaluated by Egger's linear regression and Begg's rank correlation.

The secondary objective of this review was to study the relationship between the pathological parameters of PCA and LVI. The data of pathological stage were divided as low-stage (pT2) group and high stage (pT3-4) group. Gleason scores were categorized as low Gleason score (GS <7) and high Gleason score (GS ≥7). The RR of the high stage or high Gleason score along with the corresponding 95% CI was calculated by meta-analysis. In addition, the extracapsular extension (ECE), seminal vesicle involvement (SVI), and pathological node (pN) were directly divided as positive and negative. RR and CI of positive components were analyzed. Stata (Version 12.0; Stata Corp, College station, TX, USA) was used for all statistical analyses.

RESULTS

A total of 25 studies[13–37] were selected for the systematic review and meta-analysis (**Figure 1**). With regard to the primary objective, survival outcomes with negative LVI and positive LVI were evaluated. Some studies revealed that LVI was an independent predictor in cancer-specific survival (CSS),[13,20] distant metastasis (DM),[13,22] progression-free survival (PFS),[29] overall survival (OS),[13] and these details are shown in **Supplementary Table 3**, however, the data for CSS, DM, PFS, OS were not available in any study. Nevertheless, 21 studies provided the BCR data, and the meta-analysis showed that positive LVI was correlated with poorer BCR in RP patients (HR = 2.05, 95% CI, 1.64–2.56, $P < 0.00001$) (**Figure 2**). Test of Cochrane Q ($\chi^2 = 47.39$, $P = 0.001$) and inconsistency test ($I^2 = 57.8\%$) could not exclude a significant heterogeneity. Given the large heterogeneity between the studies, subgroup analysis was performed, and the results are shown in **Supplementary Table 4**. In sensitivity analysis, one-way sensitivity analysis was carried out to exclude a single study and calculated the pooled HR for remaining studies, and omission of each study did not have a significant impact on the merged value of HR. Allowing for publication bias, Begg's funnel plot was performed, and no significant

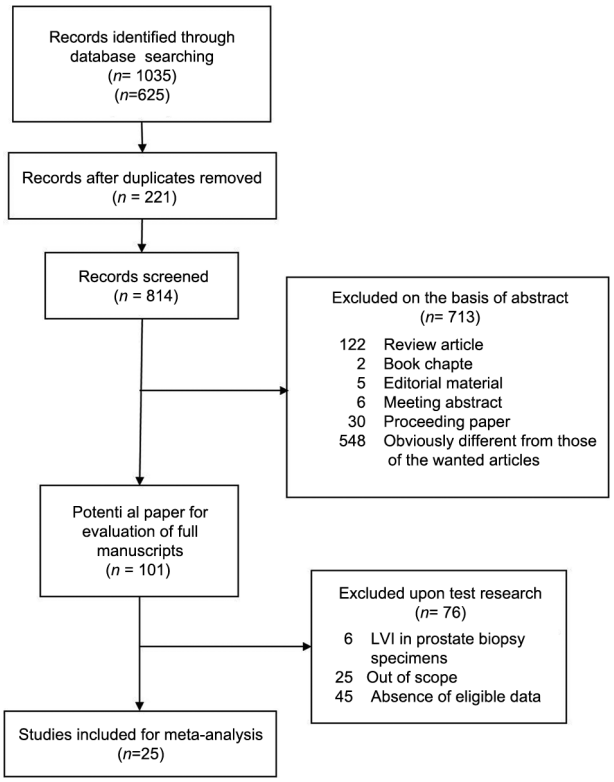

Figure 1: Flow chart of study selection.

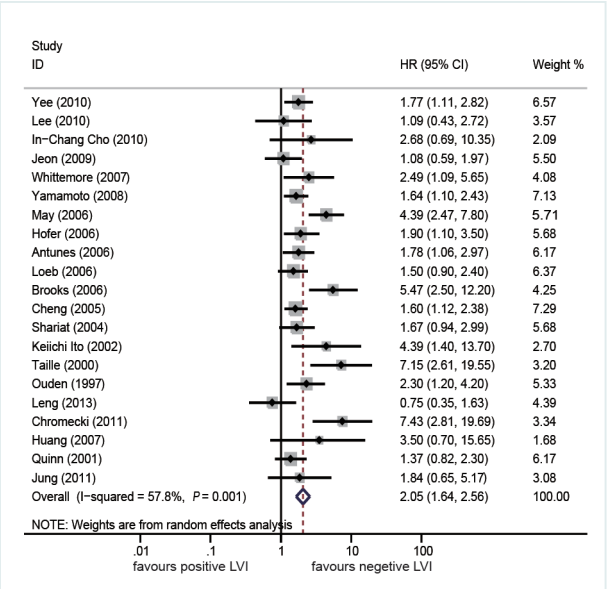

Figure 2: Forest plots of hazard ratios with the random-effects model for lymphovascular invasion in patients with prostate cancer (biochemical recurrence-free probability).

publication bias was detected between these studies regarding HR of BCR with $P = 0.112$. In addition, Egger's test ($P = 0.207$) demonstrated a similar result (**Figure 3**).

The secondary objective was to assess the relationship between LVI and higher pathological tumor stages (> pT3 stage), higher Gleason score (>GS = 7), positive pN, ECE and SVI. Ten studies provided data on the number of higher pT stage in the positive LVI groups and negative LVI groups, and the pooled RR was 1.90 (95% CI, 1.73–2.08; Z = 13.45, $P < 0.00001$) with a moderate heterogeneity ($P = 0.054$ for heterogeneity; $I^2 = 46.1\%$) (**Figure 4a**). Similarly, the data of other pathological parameters were extracted from eligible studies, and we found that LVI was significantly correlated with higher GS (pooled RR, 1.30; 95% CI, 1.23–1.39; Z = 8.55, $P < 0.00001$) with a moderate heterogeneity ($P = 0.019$ for heterogeneity; $I^2 = 47.1\%$) (**Figure 4b**), positive pN status (pooled RR, 5.67; 95% CI, 3.14–10.24; Z = 5.74, $P < 0.00001$) with a large heterogeneity ($P < 0.00001$ for heterogeneity test; $I^2 = 72.8\%$) (**Figure 4c**), ECE (pooled RR, 1.72; 95% CI, 1.46–2.02; Z = 6.50, $P < 0.00001$) with a large heterogeneity ($P < 0.00001$ for heterogeneity test; $I^2 = 73.6\%$) (**Figure 4d**) and SVI (pooled RR, 3.36; 95% CI, 2.41–4.70; Z = 7.11, $P < 0.00001$) (**Figure 4e**) despite a large heterogeneity among studies ($P < 0.00001$ for heterogeneity test; $I^2 = 81.9\%$).

DISCUSSION

Lymphovascular invasion is defined as the presence of a tumor within an endothelial-lined space,[8] which most probably links with the hematogenous spread of tumor cells. Tumor cells first infiltrate into lymphatic and/or vascular vessels, and then disseminate,[38,39] which is a much more common phenomenon in malignant tumors including PCA.[40] In addition, LVI is a significant prognostic factor in bladder, upper urinary tract urothelial and lung cancers, which has been confirmed in several systematic review studies.[41–43] As regards to liver and testicular tumors, LVI has been added to the TNM staging system, in terms of improved tumor staging.[44,45] Although the prognostic value of LVI in PCA patients after RP has been appraised by a number of studies, the results remain controversial.

The results obtained in our meta-analysis are in line with those in a previous System Review by Ng *et al*.[46] In addition, our study presented a series of advancements in comparison with the previous studies. First, we included more eligible studies with large sample sizes. The Ng's search time was ended in 2009. However, we added 8 extra studies including 2825 patients from 2009 to 2014, thus providing more exact evaluation on the effect and enabling more authentic subgroup analyses. Second, although the same result was obtained in Ng's study reporting a significant relationship between LVI and BCR in RP, we found that the pooled result of LVI had a large heterogeneity ($I^2 = 57.8\%$) by meta-analysis, and so we conducted a subgroup analysis. Meanwhile, the sensitivity analysis of our study revealed that the omission of each study did not have a significant impact on the merged value of HR. In contrast, Ng *et al*.[46] only assessed the quality of publications and no other analysis on the reliability of the result was done.

In our subgroup analyses of the region, sample size, pN status, follow-up time, negative/positive result of LVI, PSA level definition of BCR and staining method, we found a significant correlation between LVI and poor BCR. Notably, in large sample groups with the number of patients larger than 500, the pooled HR was 1.58 (1.28–1.95). In the short-term follow-up group with the follow-up duration <24 months, we also found that LVI could serve as a predictor in early BCR and be used in Nomogram for predicting BCR.[47] Although only one study[34] revealed that the addition of LVI only marginally improved the predictive accuracy (from 0.880 to 0.884). In addition, LVI was correlated with higher pT stages, higher GS, positive pN status, ECE, and SVI, indicating that the presence of LVI in PCa may predict the higher risk of progression with poor BCR, PFS, CSS, DM, and OS, and some previous studies[13,20,22,29] may support this possibility though we do not have available data to further analysis.

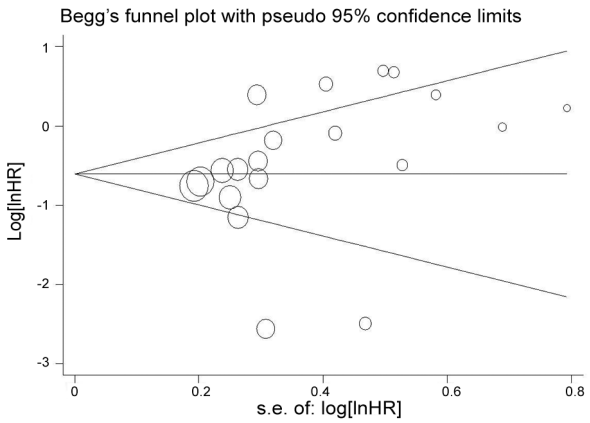

Figure 3: Begg's Funnel plots for publication bias test. Assessment of potential publication bias in studies of lymphovascular invasion in patients with prostate cancer (biochemical recurrence-free probability).

There are some limitations in our meta-analysis. The first is the problem of heterogeneity due to relevant baseline patient characteristics of each study. Although we took into account the heterogeneity in our meta-analysis using the random-effects model, the conclusion drawn in this study should be considered prudently. Second, as some of the studies were unable to provide data available to calculate HRs of BCR, we could not merge their results, although publication bias evaluation of BCR showed no significant difference and sensitivity analysis confirmed the prognostic value of LVI. In addition, as only few included studies covered survival outcomes such as PFS, CSS, DM, and OS, we were unable to perform a meta-analysis for the lack of data available to calculate HR and 95% CI directly or indirectly. Finally, most studies were retrospective, and only two studies included in our meta-analysis were prospective. Therefore, more prospective multicenter trials are required to confirm the conclusion.

In addition to these study limitation, it is usually difficult to completely exclude subjective bias among pathologists in clinical

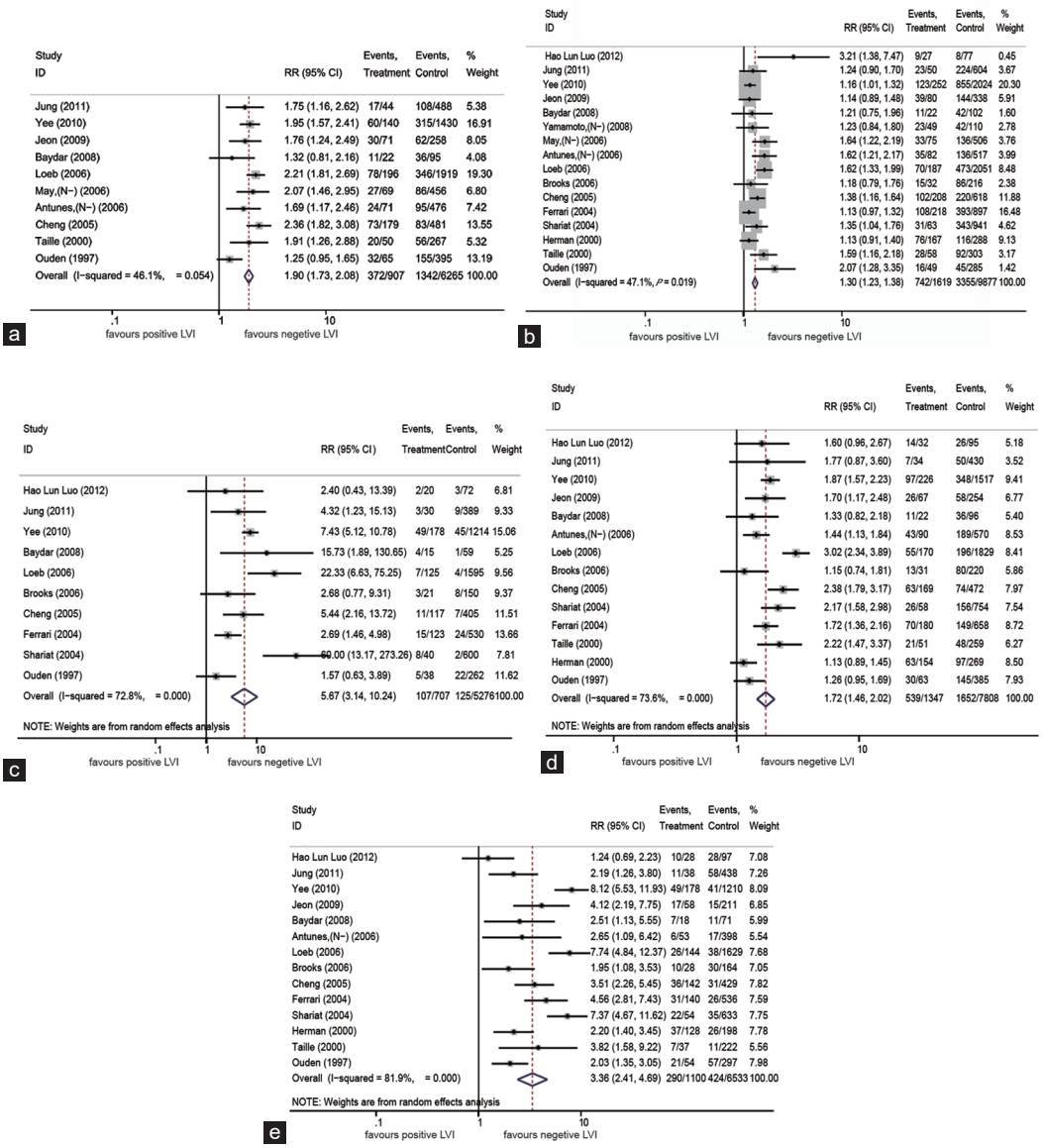

Figure 4: Forest plots of RRs for the Association of LVI with (**a**) higher pathological tumor stages (>pT3 stage); (**b**) higher Gleason score (>GS = 7); (**c**) pathological node (pN); (**d**) extracapsular extension (ECE); (**e**) seminal vesicle involvement (SVI). RR: risk ratio.

practice.[8] Knowing that the surrounding stromal tissue can mimic vascular invasion that cannot be easily be recognized, experts have reached agreement that the report of LVI is only in unequivocal cases.[27] With regard to staining method, hematoxylin and eosin (HE) is the most commonly used examination for LVI. However, some included studies incorporated immunohistochemical analysis, and this added measure may increase the detection rate of LVI.[26] But as there are still controversies over the use of immunohistochemical analysis, it is not used routinely in clinical practice. What's more, in most studies, tumor cells invasion in lymphatic vessels and vascular vessels were combined as LVI and no effort was made to distinguish between them. One reason for this is the difficulty that there is lack of reproducibility when using routine light microscopy, and previous studies have not fully evaluated the clinical values to assess the survival outcomes of prostate cancer in terms of distinguishing vascular invasion from lymphatic invasion.

CONCLUSION

Our meta-analysis indicates that LVI has a detrimental effect on the BCR-Free probability, and clinicopathological features in RP specimens and, therefore, could be considered as an independent prognostic factor of BCR. It could also be used to predict BCR patients who need further adjuvant therapies.

AUTHOR CONTRIBUTIONS

Y Huang reviewed articles, analyzed data, and drafted the manuscript; HH and XWP reviewed articles, analyzed data, and revised the manuscript critically; HH participated in as the third reviewer and drafting the manuscript; JC and Y Hong participated in data analyzing and revised the manuscript; JQY and LL participated in its design and helped to draft the manuscript; DFX supervised the project and revised manuscript; XGC and YG conceived of the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Supplementary information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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Supplementary Table 1: Main characteristics of the eligible studies

Study	*Country*	*Year*	*Institution*	*Recruitment period*	*Study design*	*Pathology stain method*	*Definition of LVI*	*Definition of BCR (ng ml^{-1})*	*Number of patients*	*Median age at operation, range (year)*	*PLND*	*Neo*	*ADT*	*EBRT*	*Median follow-up, range (months)*
Yee *et al.*[34]	USA	2010	Memorial Sloan-Kettering Cancer Center	2004–2007	Prospective	HE	Yes	PSA ≥0.1	1298	59, NA	1298	0	24	NA	27, NA
Lee *et al.*[32]	Korea	2010	Pusan National University Hospital	1999–2010	Retrospective	HE	Yes	PSA ≥0.2	361	69.0±6.8, 49–94	NA	0	0	NA	42.4±33.6, 6.5–141.6
Cho *et al.*[31]	Korea	2010	Korea Nation Cancer Center	2005–2009	Retrospective	NA	No	PSA ≥0.4	167	64.4, 49–80	NA	NA	0	NA	23.3, 2–51
Jeon *et al.*[30]	Korea	2009	Seoul Nation University Hospital	1995–2004	Retrospective	NA	Yes	PSA ≥0.2	237	64.5, 44–86	135	18	30	NA	41.4, 1–141.4
Whittemore *et al.*[28]	USA	2008	Wilford Hall Medical Center	1988–2003	Retrospective	NA	No	PSA ≥0.2	214	NA, NA	NA	0	0	0	NA, NA
Yamamoto *et al.*[29]	Japan	2008	Cancer Institute Hospital, Tokyo	1994–2005	Retrospective	HE	Yes	PSA ≥0.2	94	68, 52–76	94	0	NA	NA	47.4, 9.1–146.8
May *et al.*[26]	Germany	2006	Carl-Thiem Hospital Vivantes-Clinic Am Urban	1996–2003	Retrospective	IHC (CD31)/ HE	Yes	PSA ≥0.2	412	63.7, 44–79	412	0	0	NA	52.5, 10–116
Hofer *et al.*[23]	Germany	2005	University of Ulm Hospital	1986–2002	Retrospective	NA	Yes	PSA ≥0.4	201	64, 48–78	201	0	201	NA	41, 1–151
Antunes *et al.*[21]	Brazil	2006	Syrian Lebanese Hospital	1993–2000	Retrospective	NA	Yes	PSA ≥0.4	428	62.8, 40–83	NA	0	0	NA	53.9±20.1, NA
Loeb *et al.*[24]	USA	2006	Washington University School of Medicine North Western University Feinberg School of Medicine	1989–2002 2003–2004	Retrospective	HE	Yes	PSA ≥0.2	1709	NA, NA	NA	NA	NA	NA	34, 1–122
Brooks *et al.*[22]	USA	2005	Walter Reed Army Medical Center National Naval Medical Center	1991–2001	Retrospective	NA	No	PSA ≥0.2	160	NA, NA	160	NA	NA	32	99.6, NA
Cheng *et al.*[20]	USA	2005	Indiana University Hospital	1990–1998	Retrospective	HE	Yes	PSA ≥0.1	504	62, NA	504	0	NA	NA	44, 1.5–144
Shariat *et al.*[19]	USA	2004	University of Texas South Western Medical Center	1994–2002	Retrospective	HE	Yes	PSA ≥0.2	630	60.9, 40–75	630	NA	NA	NA	43.9, 4–100
Ito *et al.*[17]	Japan	2002	Keio University School of Medicine	1989–1998	Retrospective	HE	Yes	PSA ≥0.2	82	66.5±0.5, 56–74	82	0	0	0	21.7±1.9, 9–84.2
de la Taille *et al.*[14]	USA	1999	Columbia-Presbyterian Medical Center	1993–1998	Retrospective	HE	Yes	PSA ≥0.2	241	62, 42–77	NA	NA	NA	NA	22.9, 6–77.6
van den Ouden *et al.*[13]	Netherlands	1997	Erasmus University and Academic Hospital	1977–1994	Retrospective	HE	Yes	PSA ≥0.1	273	63.8, 45–75	273	NA	NA	NA	49, 1–206
Leng *et al.*[37]	Korea	2013	Veterans Health Service Medical Center	2005–2010	Retrospective	NA	No	PSA ≥0.2	166	NA, NA	167	0	0	0	33.7±18.7, NA
Chromecki *et al.*[35]	USA	2011	Weil Cornel Medical College	NA	Retrospective	NA	No	PSA ≥0.2	232	62.6, NA	232	0	0	0	69.0, 4.3–113.4
Quinn *et al.*[16]	Australia	2001	St. Vincent's Hospital Campus	1986–1999	Retrospective	NA	Yes	PSA ≥0.4	732	62.1, 40.7–76.7	724	83	NA	NA	41.1, 1.0–167.7
Huang *et al.*[25]	China	2007	Kaohsiung Medical University Kaohsiung Veterans General Hospital	2000–2005	Prospective	NA	No	PSA ≥0.2	126	NA, NA	NA	NA	NA	NA	NA, NA
Jung *et al.*[33]	Korea	2011	Yonsei University College of Medicine	2005–2009	Retrospective	NA	Yes	PSA ≥0.2	407	63.24, 38–82	407	0	0	0	18.43, 6–50
Ferrari *et al.*[18]	USA	2004	Stanford University Medical Center	1984–1999	Retrospective	HE	Yes	PSA ≥0.1	620	64.5, 42–78	614	0	NA	NA	90, 24–216
Luo *et al.*[36]	China	2012	Kaohsiung Chang Gung Memorial Hospital	1998–2010	Retrospective	NA	No	PSA ≥0.2	87	63, 49–83	NA	NA	NA	NA	40.9, 0.6–99.9
Herman *et al.*[15]	USA	2000	Memorial Sloan-Kettering Cancer Center	1983–1997	Retrospective	HE	Yes	PSA ≥0.4	263	64, NA	263	8	NA	NA	36, 1–158
Baydar *et al.*[27]	Turkey	2007	Hacettepe University, School of Medicine	1992–2001	Retrospective	IHC (CD31)/ HE	Yes	PSA ≥0.2	71	62, 48–75	69	0	NA	NA	54, 4–145

BCR: biochemical recurrence; PSA: prostate specific antigen; EBRT: external beam radiotherapy; RP: radical prostatectomy; ADT: androgen deprivation therapy; PLND: pelvic lymph node dissection; Neo: neoadjuvant; HE: hematoxylin and eosin; IHC: immunohistochemistry; NA: not available; LVI: lymphovascular invasion

Supplementary Table 2: The TNM stage characteristics and correlations between LVI and preoperative PSA and pathological parameters

Study	*TNM stages and GS characteristics (staging system)*	*Number (%) of positive LVI*	*Preoperative PSA (ng ml^{-1})*			*pT stage ≥pT3/total*		*ECE Positive/total*		*SVI Positive/total*		*GS ≥7 GS/total*		*pN stage pN+/total*	
			LVI (+)	*LVI (–)*	*P**	*LVI (+)*	*LVI (–)*	*LVI (+)*	*LVI (–)*	*LVI (+)*	*LVI (–)*	*LVI (+)*	*LVI (–)*	*LVI (+)*	*LVI (–)*
Yee *et al.*[34]	pT2-4, pN0-1 GS (<7, 7, >7) (2002 AJCC)	129/1298 (9.9)	7.3 (4.9–11.3)	5.1 (3.7–7.1)	<0.001	60/80	315/1115	97/129	348/1169	49/129	41/1169	123/129	855/1169	49/129	45/1169
Lee *et al.*[32]	pT2-4, pN0-1 GS (<7, 7, >7) (2002 AJCC)	40/361 (11.1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cho *et al.*[31]	pT2-3, pNx GS (<7, 7, >7) (2002 AJCC)	16/167 (9.6)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jeon *et al.*[30]	pT2-3, pN0-1 GS (<7, 7, >7) (2002 AJCC)	41/237 (17.3)	16.4 (2.7–98.0)	10.5 (0.2–86.6)	0.002	30/41	62/196	26/41	58/196	17/41	15/196	39/41	144/194	NA	NA
Whittemore *et al.*[28]	pT2-4, pN0-1 GS (7) (2002 AJCC)	12/214 (5.6)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yamamoto *et al.*[29]	pT3a, pN0 GS (<7, 7, >7) (1997 AJCC)	26/94 (27.7)	12.8 (3.5–59.0)	8.55 (0.5–75.0)	0.022	26/26	94/94	NA	NA	0/26	0/68	23/26	42/68	0/26	0/68
May *et al.*[26]	pT2-3b, pN0 GS (<7, 7, >7) (1997 AJCC)	42/412 (10.2)	22.6 (6.4–151)	10.9 (0.1–51)	<0.001	27/42	86/370	NA	NA	NA	NA	33/42	136/370	0/42	0/370
Hofer *et al.*[23]	pTx, pN1 GS (<7, 7, >7) (2002 AJCC)	29/116 (25.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	29/29	116/116
Antunes *et al.*[21]	pT2-3, pN0 GS (<7, 7, >7) (1992 AJCC)	47/428 (11.0)	10.6 (8.6–13.1)	8 (7.5–8.5)	0.004	24/47	95/381	43/47	189/381	6/47	17/381	35/47	136/381	0/47	0/381
Loeb *et al.*[24]	pTx, pN0-1 GS (<7, 7, >7) (NA)	118/1709 (6.9)	5.8	4.5	<0.0001	78/118	346/1573	55/115	196/1633	26/118	38/1591	70/117	473/1578	7/118	4/1591
Brooks *et al.*[22]	pTx, pN0-1 GS (<7, 7, >7) (NA)	18/160 (11.3)	10.9 (4.7–40.7)	17.7 (1.3–217)	0.44	NA	NA	13/18	80/140	10/18	30/134	15/17	86/130	3/18	8/142
Cheng *et al.*[20]	pT2-3, pN0-1 GS (<7, 7, >7) (1997 AJCC)	106/504 (21.0)	NA	NA	NA	73/106	83/398	63/106	74/398	36/106	31/398	102/106	220/398	11/106	7/398
Shariat *et al.*[19]	pTx, pN0-1 GS (<7, 7, >7) (1997 AJCC)	32/630 (5.1)	7.8 (4.0–99.0)	6.0 (0.1–52.0)	0.04	NA	NA	26/32	156/598	22/32	35/598	31/32	343/598	8/32	2/598
Ito *et al.*[17]	pT2-3, pN0 GS (<7, 7, >7) (1997 AJCC)	38/82 (46.3)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/38	0/44
de la Taille *et al.*[14]	pT2-3, pN0-1 GS (<7, 7, >7) (NA)	30/241 (12.4)	NA	NA	NA	20/30	56/211	21/30	48/211	7/30	11/211	28/30	92/211	NA	NA
van den Ouden *et al.*[13]	pT2-4, pN0-1 GS (<7, 7, >7) (1992 AJCC)	33/273 (12.1)	NA	NA	NA	32/33	155/240	30/33	145/240	21/33	57/240	16/33	45/240	5/33	22/240
Leng *et al.*[37]	pT2-4, pN0-1 GS (7) (2010 AJCC)	40/166 (24.1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chromecki *et al.*[35]	pTx, pN0-1 GS (<7, 7, >7) (NA)	8/102 (7.8)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quinn *et al.*[16]	pT2-4, pN0-1 GS (<7, 7, >7) (1992 AJCC)	38/731 (5.2)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Huang *et al.*[25]	pT2-4, pN0-1 GS (<7, 7, >7) (1997 AJCC)	17/111 (15.3)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jung *et al.*[33]	pT2-3, pN0-1 GS (<7, 7, >7) (2002 AJCC)	27/407 (6.6)	12.83 (2.40–30.78)	9.83 (1.76–83.23)	0.075	17/27	108/380	7/27	50/380	11/27	58/380	23/27	224/380	3/27	9/380
Ferrari *et al.*[18]	pTx, pN0-1 GS (<7, 7, >7) (NA)	110/620 (17.7)	NA	NA	NA	NA	NA	70/110	149/509	31/109	26/510	108/110	393/504	15/108	24/506
Luo *et al.*[36]	pTx, pN0-1 GS (<7, 7, >7) (NA)	18/87 (20.7)	NA	NA	NA	NA	NA	14/18	26/69	10/18	28/69	9/18	8/69	2/18	3/69
Herman *et al.*[15]	pT3, pN0 GS (<7, 7, >7) (NA)	91/172 (52.9)	NA	NA	NA	NA	NA	63/91	97/172	37/91	26/172	76/91	116/172	0/91	0/172
Baydar *et al.*[27]	pT2-3, pN0-1 GS (<7, 7, >7) (NA)	11/71 (15.5)	NA	NA	NA	11/11	36/60	11/11	36/59	7/11	11/60	11/11	42/60	4/11	1/58

*A *P* value represent a statistically difference. TNM: tumor-node-metastasis; ECE: extracapsular extension; SVI: seminal vesicle involvement; LVI: lymphovascular invasion; PSA: prostate-specific antigen; pT: pathological tumor; pN: pathological node; AJCC: American Joint Committee on Cancer and the International Union Against Cancer; GS: Gleason score; NA: not available

Supplementary Table 3: Estimation of the HR

Study	*Survival analysis*	*HR estimation or P*	*Co-factors*	*LVI independent predictor?*
Yee *et al.*[34]	BCR	HR (95% CI): 1.77 (1.11–2.82)	Pre-PSA, ECE, SVI, GS, SM, LNI	Yes
Lee *et al.*[32]	BCR	HR (95% CI): 1.086 (0.434–2.716)	GS, pT stage, SM, TV Primary-Gleason grade, secondary-Gleason grade Number of positive lymph nodes, nadir PAS	No
	CSS	*P=0.533	NA	No
Cho *et al.*[31]	BCR	HR (95% CI): 2.683 (0.695–10.353)	Pre-PSA, biopsy GS, GS, SM, ECE, SVI, Bcl-2 expression	No
Jeon *et al.*[30]	BCR	HR (95% CI): 1.08 (0.59–1.97)	Pre-PSA, ECE, SVI, GS, SM, PNI	No
Whittemore *et al.*[28]	BCR	HR (95% CI): 2.49 (1.09–5.65)	>pT2 stage, pre-PSA, SM, PNI, LNI, percentage cancer (tumor burden) Primary Gleason pattern 4, tertiary Gleason pattern 5	Yes
Yamamoto *et al.*[29]	BCR	HR (95% CI): 1.64 (1.1–2.43)	Pre-PSA, biopsy GS, GS, SM, clinical stage	Yes
	PFS	*P=0.027	NA	Yes
May *et al.*[26]	BCR	HR (95% CI): 4.39 (2.47–7.80)	Pre-PSA, GS, SVI, PSA density, positive biopsy cores	Yes
Hofer *et al.*[23]	BCR	HR (95% CI): 1.9 (1.1–3.5)	Gleason grade 4/5, nuclear grade 3	Yes
Antunes *et al.*[21]	BCR	HR (95% CI): 1.78 (1.06–2.97)	Pre-PSA, ECE, SM, clinical stage, present of positive biopsy cores	Yes
Loeb *et al.*[24]	BCR	HR (95% CI): 1.5 (0.9–2.4)	GS, SVI, SM, ECE, LNI	No
Brooks *et al.*[22]	BCR	HR (95% CI): 5.47 (2.5–12.2)	Pre-PSA, SM, LNI, ECE, SVI, GS, PNI Undetectable PSA after RP, pre-RP PSA level Hormones during treatment, RT dose, salvage versus adjuvant RT Interval from RP to P-XRT (median, >316 days median value)	Yes
	DM	*P<0.001	NA	Yes
Cheng *et al.*[20]	BCR	HR (95% CI): 1.6 (1.12–2.38)	pT stage, GS, SM	Yes
	CSS	*P<0.001	NA	Yes
Shariat *et al.*[19]	BCR	HR (95% CI): 1.671 (0.935–2.986)	Pre-PSA, LNI, PNI, ECE, SVI, GS, SM	No
Ito *et al.*[17]	BCR	HR (95% CI): 4.39 (1.40–13.70)	GS, ECE, SM, SVI, PNI	Yes
de la Taille *et al.*[14]	BCR	HR (95% CI): 7.15 (2.61–19.55)	pT3 stage, pre-PSA, GS, SM	Yes
van den Ouden *et al.*[13]	BCR	HR (95% CI): 2.3 (1.2–4.2)	ECE, grade 3, positive lateral margin	Yes
	OS	*P=0.02	NA	Yes
	CSS	*P<0.001	NA	Yes
	DM	*P<0.001	NA	Yes
Leng *et al.*[37]	BCR	HR (95% CI): 0.75 (0.35–1.63)	>pT2 stage, PSA density, TV, SM, PNI Primary Gleason pattern 4, tertiary Gleason pattern 5	No
Chromecki *et al.*[35]	BCR	HR (95% CI): 7.435 (2.808–19.686)	pT stage, pre-PSA, LNI, ECE, SVI, GS, SM, abnormal IMP3	Yes
Quinn *et al.*[16]	BCR	HR (95% CI): 1.37 (0.82–2.30)	pT stage, pre-PSA, GS, SVI, LNI, PNI, SM, year of RP, adjuvant therapy (excluding indefinite hormonal therapy)	No
Huang *et al.*[25]	BCR	HR (95% CI): 3.51 (0.79–15.65)	Pre-PSA, GS, PNI, SM, age, tumor mulifocality, HGPIN p53 codon72 Arg/Arg versus (Arg/Pro+Pro/Pro) XPCC1 codon 194 (Arg/Trp+Trp/Trp) versus Arg/Arg XPCC1 codon 280 (Arg/His+His/His) versus Arg/Arg XPCC1 codon 399 (Arg/Gln+Gln/Gln) versus Arg/Arg	No
Jung *et al.*[33]	BCR	HR (95% CI): Univariate 1.839 (0.654–5.172)	Pre-PSA, SVI, GS, SM, ECE, LNI, PNI, HGPIN	No
Luo *et al.*[36]	BCR	NA	NA	Yes
Baydar *et al.*[27]	BCR	NA	NA	Yes
Ferrari *et al.*[18]	BCR	NA	NA	Yes
Herman *et al.*[15]	BCR	NA	NA	Yes

*A *P* value was determined by the log rank test. BCR: biochemical recurrence-free survival; GS: Gleason score; ECE: extracapsular extension; SVI: seminal vesicle invasion; LNI: lymph node invasion; SM: surgical margins; TV: tumor volume; PNI: perineural invasion; PSA: prostate-specific antigen; IMP3: insulin-like growth factor II mRNA binding protein 3; HGPIN: high-grade prostatic intraepithelial neoplasia; XRCC1: X-ray repair cross-complementing protein-1; PTLD: peritumoral lymphatic vessel density; RP: radical prostatectomy; P-XRT: postprostatectomy radiotherapy; RT: radiotherapy; PFS: progression-free survival; DM: distant metastases; OS: over survival; CSS: cancer specific survival; HR: hazard ratio; NA: not available; LVI: lymphovascular invasion; CI: confidence interval; PAS: periodic acid-Schiff

Supplementary Table 4: Subgroup analysis of biochemical recurrence-free survival

	Number of included articles	*Number of cases*	*Pooled HR (95% CI)*	*ES*	*Heterogeneity*	*P (het)*	*Publication bias*	
					I^2 *(%)*		*Begg's P*	*Egger's P*
Region								
Asian	8	1625	1.479 (1.139–1.921) Fix, (inverse variance)	*Z*=2.94 *P*=0.003	32.2	0.171	0.108	0.405
Other	13	6818	2.322 (1.771–3.043) Random, (inverse variance)	*Z*=6.10 *P*<0.001	62.9	0.001	0.035	0.058
Number of patients								
<200	8	998	2.590 (1.539–4.360) Fix, (inverse variance)	*Z*=3.58 *P*=0.000	69.2	0.002	0.386	0.209
200–500	8	2771	2.219 (1.454–3.387) Random, (inverse variance)	*Z*=3.69 *P*=0.000	63.7	0.007	0.902	0.757
>500	5	4872	1.582 (1.281–1.953) Fix, (inverse variance)	*Z*=4.27 *P*=0.000	0.0	0.963	-	-
Pathologic N stage								
pN–	4	1016	2.493 (1.471–4.224) Random, (inverse variance)	*Z*=3.39 *P*=0.001	69.1	0.021	-	-
pN+	1	116	1.9 (1.1–3.5)	NA	NA	NA	NA	NA
Median follow-up								
≤24 months	4	897	3.645 (2.091–6.353) Fix, (inverse variance)	*Z*=4.56 *P*=0.000	19.0	0.295	-	-
24–36 months	3	3173	1.442 (1.059–1.965) Fix, (inverse variance)	*Z*=2.32 *P*=0.020	43.5	0.170	-	-
>36 months	12	4048	2.031 (1.536–2.685) Random, (inverse variance)	*Z*=4.97 *P*=0.000	64.3	0.001	0.902	0.511
LVI independent predictor?								
No	9	4519	1.374 (1.088–1.734) Fix, (inverse variance)	*Z*=2.67 *P*=0.008	0.0	0.598	0.536	0.496
Yes	12	3924	2.618 (1.953–3.509) Random, (inverse variance)	*Z*=6.44 *P*=0.000	63.3	0.002	0.019	0.038
Definition of BCR								
PSA≥0.1	3	2075	1.765 (1.353–2.301) Fix, (inverse variance)	*Z*=4.19 *P*=0.000	0.0	0.623	-	-
PSA≥0.2	14	4926	2.311 (1.610–3.318) Random, (inverse variance)	*Z*=4.54 *P*=0.000	70.2	0.000	0.902	0.544
PSA≥0.4	4	1442	1.691 (1.252–2.285) Fix, (inverse variance)	*Z*=3.43 *P*=0.001	0.0	0.733	-	-
Stain method								
HE	9	5192	1.776 (1.483–2.128) Fix, (inverse variance)	*Z*=6.23 *P*=0.000	35.9	0.131	0.386	0.117
IHC and HE	1	412	4.39 (2.47–7.8)	NA	NA	NA	NA	NA

PSA: prostate-specific antigen; BCR: biochemical recurrences; HE: hematoxylin and eosin; IHC: immunohistochemistry; HR: hazard ratio; CI: confidence interval; LVI: lymphovascular invasion; ES: effect size; NA: not available