Predictive Factors for Positive Surgical Margins in Patients With Prostate Cancer After Radical Prostatectomy: A Systematic Review and Meta-Analysis

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Background and Objectives: Previous studies have demonstrated that positive surgical margins (PSMs) were independent predictive factors for biochemical and oncologic outcomes in patients with prostate cancer (PCa). This study aimed to conduct a meta-analysis to identify the predictive factors for PSMs after radical prostatectomy (RP).

Methods: We selected eligible studies via the electronic databases, such as PubMed, Web of Science, and EMBASE, from inception to December 2020. The risk factors for PSMs following RP were identified. The pooled estimates of standardized mean differences (SMDs)/odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A fixed effect or random effect was used to pool the estimates. Subgroup analyses were performed to explore the reasons for heterogeneity.

Results: Twenty-seven studies including 50,014 patients with PCa were eligible for further analysis. The results showed that PSMs were significantly associated with preoperative prostate-specific antigen (PSA) (pooled SMD = 0.37; 95% CI: 0.31–0.43; P < 0.001), biopsy Gleason Score (<6/≥7) (pooled OR = 1.53; 95% CI:1.31–1.79; P < 0.001), pathological Gleason Score (<6/≥7) (pooled OR = 2.49; 95% CI: 2.19–2.83; P < 0.001), pathological stage (<T2/≥T3) (pooled OR = 3.90; 95% CI: 3.18–4.79; P < 0.001), positive lymph node (PLN) (pooled OR = 3.12; 95% CI: 2.28–4.27; P < 0.001), extraprostatic extension (EPE) (pooled OR = 4.44; 95% CI: 3.25–6.09; P < 0.001), and seminal vesicle invasion (SVI) (pooled OR = 4.19; 95% CI: 2.87–6.13; P < 0.001). However, we found that age (pooled SMD = 0.01; 95% CI: −0.07–0.10; P = 0.735), body mass index (BMI) (pooled SMD = 0.12; 95% CI: −0.05–0.30; P = 0.162), prostate volume (pooled SMD = −0.28; 95% CI: −0.62–0.05; P = 0.097), and nerve sparing (pooled OR = 0.90; 95% CI: 0.71–1.14; P = 0.388) had no effect on PSMs after RP. Besides, the findings in this study were found to be reliable by our sensitivity and subgroup analyses.

Conclusions: Preoperative PSA, biopsy Gleason Score, pathological Gleason Score, pathological stage, positive lymph node, extraprostatic extension, and seminal vesicle invasion are significant predictive factors of PSMs after radical prostatectomy.
INTRODUCTION

Prostate cancer (PCa) is the most common type of newly diagnosed malignancy and a leading cause of cancer-related death in males worldwide (1). With the wide use of the prostate-specific antigen (PSA) screening test, the majority of PCa patients are diagnosed in the early stages (2). As a result, radical prostatectomy (RP) with bilateral pelvic lymph node dissection has been the gold standard for the treatment of patients with localized PCa (3). The goal of RP for PCa is complete prostate extirpation; despite favorable cancer control associated with RP, approximately 25% of all patients experience biochemical recurrence (BCR) (4). A number of factors have been found to be associated with BCR after RP, and one adverse risk factor is the presence of positive surgical margins (PSMs).

PSMs are defined as an extension of cancer cells to the inked cut surface of the RP specimen (5). Our previous findings have indicated that PSMs are significantly associated with BCR and poor survival outcome after RP (6, 7). However, none of the systematic research studies have reported about the factors that may affect the margin status of PCa after RP. Conventional parameters for risk estimation of PSMs are mainly based on factors, including preoperative PSA (p-PSA), pathological T stage, pathological Gleason Score (GS), and multiple positive biopsy cores (8–11). However, the prognostic value of these predictive factors is limited. Besides, PSMs may be affected by remnant normal tissue and inadequate surgical skill (12). Therefore, no consensus has been reported regarding the above results. Based on these considerations, a comprehensive meta-analysis and systematic review was necessary to evaluate the predictive factors for PSMs in PCa patients following RP.

MATERIALS AND METHODS

Literature and Search Strategy

We carried out this meta-analysis in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) (13). A comprehensive literature search was conducted using the PubMed, Web of Science, Wanfang, and China National Knowledge Infrastructure (CNKI) databases. Search strategies were based on the combination of Medical Subject Headings (MeSH) and keywords as follows: “prostate cancer,” “radical prostatectomy,” “positive surgical margin,” “clinicopathological” and “risk factors.” The last search was conducted on December 2020. Meanwhile, to identify other eligible publications, reference lists were also screened manually. The language was restricted to English and Chinese. Because we did not perform clinical research in this study, no ethical approval was needed and all analyses were based on previously published literatures.

Selection Criteria and Data Extraction

Papers were included in this meta-analysis if they met the following criteria: (1) all patients with a diagnosis of PCa and PSMs were histopathologically confirmed; (2) treatment was limited to RP; (3) clinicopathological features were analyzed according to the surgical margins status, and all studies had a comparable study design; (4) standardized mean differences (SMDs)/odds ratios (ORs) and 95% confidence intervals (CIs) were reported in the paper or could be computed from the given data; (5) if more than one article was identified in the same cohort, the most comprehensive and largest dataset was adopted. Accordingly, studies with the following criteria were excluded: (1) case reports, review articles, editorials, and non-original articles; (2) papers not published in English and Chinese; (3) studies that did not analyze the PSMs and clinical features; (4) studies lacking sufficient data to acquire SMDs/ORs and 95% CIs. Literature search was independently performed by two investigators. Disagreement was resolved by discussion.

Data Extraction and Quality Assessment

Two researchers (BW and ZZ) assessed the titles and abstracts of the searched studies, respectively. Any disagreements were reconciled by a third researcher (JY). The following information was extracted from the included studies: publication information (first author’s last name, publication year, country of origin, and study design), patients’ characteristics (mean age, p-PSA, and follow-up time), and PCa outcomes (tumor stage, GS, and oncologic outcomes). According to the Newcastle–Ottawa quality assessment scale (NOS) (14), two researchers (HZ and YF) independently assessed the quality of each study. According to its criteria, the NOS estimates studies based on the following three parts: selection, comparability, and outcome assessment. For quality assessment, scores ranged from 0 to 9, and studies with scores of 6 or more were rated as being of high quality.

Statistical Analysis

For this meta-analysis, pooled SMDs/ORs with 95% CIs were used to describe the relationship between risk factors and PSMs. An OR >1 or SMD >0 suggested a close relationship of PSMs in patients with PCa. Heterogeneity among studies was evaluated by using Cochran’s Q test and Higgins I²-squared statistic. If the I² value was >50% or the P heterogeneity was <0.1, it suggested a statistically significant heterogeneity in the included studies, and a random-effects (RE) model was adopted; otherwise, a fixed-effects (FE) model was used.
was used. To consider the potential reason for heterogeneity, subgroup analysis was conducted. To test the stability of the result, we performed a sensitivity analysis by excluding one study in turn. Visual inspection of asymmetry in funnel plots was carried out to assess the potential publication bias. Furthermore, we performed Egger’s tests to provide quantitative evidence of publication bias. These statistical analyses or data syntheses were calculated using STATA version 12.0 (Stata Corporation, College Station, TX, USA). All statistical tests were two sided, and P < 0.05 was considered statistically significant.

RESULTS

Literature Search

A flowchart of the literature selection process is shown in Figure 1. The initial search of electronic databases identified 1,568 records according to the search criteria; after the duplicates were removed, 883 papers remained behind. A total of 588 papers were then excluded by screening the titles and abstracts. Then, 295 full-text articles were further examined and 268 articles were excluded because 27 articles included the same cohort of patients and 241 articles lacked enough data for further research. Finally, 27 articles (8, 15–40) published between 2009 and 2020 were included in this meta-analysis.

Features of the Included Studies

Summary of the major characteristics of these studies is shown in Table 1 and Table 2. All studies had a retrospective study design. The sample size ranged from 144 to 12,515, and a total of 50,014 patients were included. A total of 12,093 PCa patients with PSMs were included in our study, which accounted for 24.2% of all patients. Geographically, eight studies were conducted in Asia, eight in North America, eight in Europe, two in Australia, and one in multi-center locations. All patients had received RP as primary treatment for PCa. According to the NOS quality assessment, all studies included in this study were categorized as being of high quality (Supplementary Table S1).
### TABLE 1 | The basic characteristics of all studies included in this meta-analysis.

| Author            | Year | Country | Recruitment period | No. of patients | Age (years) PSMs | Age (years) NSMs | Pre-PSA PSMs | Pre-PSA NSMs | Follow-up (months) | PSMs | NSMs |
|-------------------|------|---------|--------------------|-----------------|------------------|-----------------|--------------|--------------|-------------------|------|------|
| Celik et al. (15) | 2020 | Turkey  | 2005–2020          | 893             | Mean ± SD        | Mean ± SD       | Mean ± SD    | 13 ± 18.9    | Mean ± SD            | 8.8 ± 9.5 | NA    |
| Porcaro et al. (16)| 2020 | Italy   | 2013–2017          | 192             | Median (IQR)     | Median (IQR)    | Mean ± SD    | Median (IQR) | 6.9 (5.1–8.7)        | 6.1 (4.8–8.3) | 26 (14–40) |
| Tian et al. (17)  | 2019 | China   | 2010–2016          | 142             | Median (IQR)     | Median (IQR)    | Mean ± SD    | Median (IQR) | 13.7 (9.3–25.0)      | 10.2 (6.7–17.7) | NA    |
| Martini et al. (18)| 2019 | Italy   | 2011–2017          | 285             | Median (IQR)     | Median (IQR)    | Mean ± SD    | Median (IQR) | 7.2 (5.5–10.6)       | 6.3 (4.6–8.3) | Median |
| Hou et al. (19)   | 2019 | China   | 2007–2017          | 94              | Median (IQR)     | Median (IQR)    | Mean ± SD    | Median (IQR) | 14.4 (1–123)         | 14.4 (1–123) | 9 (1–83) |
| Herforth et al. (20)| 2018 | USA     | 1988–2015          | 1,902           | Median (IQR)     | Median (IQR)    | Mean ± SD    | Median (IQR) | 7.5 (5.2–12)         | 5.9 (4.4–5.5) | 93 (53–152) |
| Tatsugami et al. (21)| 2017| Japan   | 2009–2013          | 594             | Median (IQR)     | Median (IQR)    | Mean ± SD    | Median (range) | 6.6 (1.8–57.1)       | 7.7 (3.0–69.8) | 105 (63–147) |
| Seo et al. (8)    | 2017 | Korea   | 2008–2014          | 50              | Mean ± SD        | Mean ± SD       | Mean ± SD    | Mean ± SD    | Mean ± SD            | 16.3 ± 11.4 | 10.5 ± 6.7 |
| Meyer et al. (22) | 2017 | USA     | 1992–2005          | 118             | Median (IQR)     | Median (IQR)    | Mean ± SD    | Mean ± SD    | Mean ± SD            | 6 (4.3–9.0)  | Median |
| Abdollah et al. (23)| 2016| MC      | 2002–2013          | 1,045           | Median (IQR)     | Median (IQR)    | Mean ± SD    | Mean ± SD    | Mean ± SD            | 6.4 (4.6–8.9) | Median |
| Whalen et al. (24) | 2015 | USA     | 2005–2011          | 126             | Mean ± SD        | Mean ± SD       | Mean ± SD    | Mean ± SD    | Mean ± SD            | 9.2 ± 8.6    | 6.1 ± 5.4 |
| Retèl et al. (25) | 2014 | Switzerland | 1990–2008       | 479             | Mean ± SD        | Mean ± SD       | Mean ± SD    | Mean ± SD    | Mean ± SD            | 8.5 ± 13.4   | Median |
| Rouanne et al. (26)| 2014| France  | 1988–2001          | 108             | Median (range)   | Median (range)  | Median (range) | Median (range) | 10 (2–158)          | 10 (0.5–134) | 73.2 (2–120) |
| Sammon et al. (27) | 2013 | USA     | 1993–2010          | 162             | Mean ± SD        | Mean ± SD       | Mean ± SD    | Mean ± SD    | Mean ± SD            | 6.9 ± 4.6    | 5.3 ± 3.3 |
| Lee et al. (28)   | 2013 | Korea   | 2005–2011          | 167             | Mean ± SD        | Mean ± SD       | Mean ± SD    | Mean ± SD    | Mean ± SD            | 8.4 ± 6.4    | NA    |
| Hashimoto et al. (29) | 2013| Japan   | 2006–2011          | 54              | Mean ± SD        | Mean ± SD       | Mean ± SD    | Mean ± SD    | Mean ± SD            | 9.3 ± 7.3    | NA    |
| Abdollah et al. (30) | 2013| Italy   | 1998–2010          | 305             | Mean ± SD        | Mean ± SD       | Mean ± SD    | Mean ± SD    | Mean ± SD            | 6.2 (0.2–47.8) | 122.5  |

(Continued)
| Author          | Year | Country     | Recruitment period | No. of patients | Age (years) | Pre-PSA | Follow-up (months) |
|-----------------|------|-------------|--------------------|-----------------|-------------|---------|-------------------|
| Savdie et al. (31) | 2012 | Australia   | 1997–2003          | 285             | Median (range) 61.7 (46.4–81) | Median (range) 8.7 (2–63) | Median (range) 82 (5–146) |
| Lu et al. (32)   | 2012 | China       | 1993–1999          | 250             | Median (IQR) 61.2 (42.2–77.4) | Median (IQR) 6.2 (4.5–9.3) | Median (IQR) 115.2 (72–132) |
| Karavitakis et al. (33) | 2012 | UK          | 2007–2009          | 31              | Mean 62.9 | Mean 13.9 | NA |
| Concoran et al. (34) | 2012 | Australia   | 1995–2010          | 370             | Median (range) 61.5 (40.2–79.8) | Median (range) 7.8 ± 6.6 | Median (range) 22.2 (0.8–181) |
| Li et al. (35)   | 2011 | China       | 2000–2009          | 57              | Mean ± SD 70.2 ± 6.3 | Mean ± SD 13.4 ± 17.6 | Mean ± SD 46.8 ± 27.8 |
| Coelho et al. (36) | 2010 | USA         | 2008–2009          | 101             | Median (IQR) 62 (56–66) | Median (IQR) 5 (3.9–6.9) | Median (IQR) 22.2 (0.8–181) |
| Boorjan et al. (37) | 2010 | USA         | 1990–2006          | 3,651           | Median (IQR) 64 (59–69) | Median (IQR) 8.1 (5.4–14.1) | Median (IQR) 98.4 (52.8–145.2) |
| Alkhateeb et al. (38) | 2010 | Canada      | 1992–2008          | 264             | Mean ± SD 62 ± 6.6 | Mean ± SD 7.7 (0.1–65.9) | Mean ± SD 78.1 (3–192) |
| Shikanov et al. (39) | 2009 | USA         | 2003–2008          | 243             | Median (IQR) 59 (54–65) | Median (IQR) 5.6 (4.4–8.1) | Median (IQR) 12.3 (6.3–18.9) |
| Ficarra et al. (40) | 2009 | Italy       | 2005–2008          | 95              | Mean 61.4 | Mean 5.1 (4.1–7.1) | Median 14 |

SD, standard deviation; NA, data not applicable; MC, Multi-centers; PSMs, positive surgical margins; NSMs, negative surgical margins.
### TABLE 2 | The main pathological characteristics of all studies included in this meta-analysis.

| Author & Year | Staging System | Grading System | Biopsy GS <6/7 | Pathological GS <6/7 | Pathological stage 1–2/3–4 |
|---------------|----------------|----------------|----------------|----------------------|---------------------------|
|               |                |                | PSNs | NSMs | PSNs | NSMs | PSNs | NSMs | PSNs | NSMs |
| Celik et al. (15) | TNM | 2014 ISUP | NA | NA | NA | NA | 427/466 | 1,377/413 |
| Porcari et al. (16) | 2010 TNM | 2014 ISUP | 81/111 | 262/278 | 19/173 | 107/233 | 161/31 | 453/87 |
| Tian et al. (17) | 2012 TNM | ISUP | NA | NA | NA | NA | 75/67 | 212/64 |
| Martin et al. (18) | TNM | Gleason score | NA | NA | 203/82 | 1,246/208 | 108/177 | 969/503 |
| Hou et al. (19) | TNM | Gleason score | 27/67 | 101/125 | 16/78 | 84/142 | 46/48 | 174/52 |
| Herforth et al. (20) | TNM | Gleason score | NA | NA | NA | NA | 1,249/653 | 1,567/496 |
| Tatsugami et al. (21) | TNM | Gleason score | 172/422 | 1,200/594 | 46/548 | 276/1,518 | 539/55 | 62/594 |
| Seo et al. (8) | TNM | Gleason score | 14/36 | 40/54 | NA | NA | 34/16 | 84/10 |
| Meyer et al. (22) | 2002 TNM | Gleason score | 98/20 | 625/120 | 69/49 | 510/275 | NA | NA |
| Abdollah et al. (23) | TNM | Gleason score | 436/891 | 1,726/2,237 | 139/1,198 | 1,167/2,796 | 373/954 | 2,683/1,080 |
| Whalen et al. (24) | 1997 TNM | Gleason score | 30/96 | 214/239 | 30/96 | 214/239 | 51/75 | 365/88 |
| Retel et al. (25) | TNM | Gleason score | NA | NA | 224/255 | 502/273 | 239/240 | 629/146 |
| Rouanne et al. (26) | TNM | Gleason score | 81/27 | 233/62 | 49/59 | 181/114 | 35/73 | 224/71 |
| Sammon et al. (27) | TNM | Gleason score | 67/95 | 525/107 | 47/115 | 298/334 |
| Lee et al. (28) | TNM | Gleason score | NA | NA | 30/136 | 63/193 | 88/79 | 169/31 |
| Hashimoto et al. (29) | NA | Gleason score | 18/36 | 63/127 | NA | NA | NA | NA |
| Abdollah et al. (30) | TNM | Gleason score | NA | NA | 115/190 | 635/563 | 256/49 | 1,115/83 |
| Savdie et al. (31) | TNM | Gleason score | NA | NA | 75/210 | 241/414 | 105/180 | 438/217 |
| Lu et al. (32) | TNM | Gleason score | NA | NA | 80/170 | 293/251 | 161/89 | 468/76 |
| Karavitakis et al. (33) | TNM | Gleason score | 18/13 | 43/21 | 7/21 | 22/43 | 14/17 | 45/19 |
| Corcoran et al. (34) | TNM | Gleason score | NA | NA | 47/323 | 290/854 | 182/188 | 924/220 |
| Li et al. (35) | 1992 TNM | Gleason score | NA | NA | 21/80 | 310/463 | 43/58 | 669/106 |
| Coelho et al. (36) | TNM | Gleason score | 56/45 | 453/322 | 21/80 | 310/463 | NA | NA |
| Boorjani et al. (37) | TNM | Gleason score | 1,905/1,125 | 5,372/1,621 | 1,806/1,839 | 5,719/2,328 | 2,072/1,579 | 6,767/1,289 |
| Alkhateeb et al. (38) | TNM | Gleason score | NA | NA | 42/222 | 310/694 | 116/148 | 737/267 |
| Shikanov et al. (39) | TNM | Gleason score | 118/125 | 727/428 | 73/170 | 592/563 | 120/123 | 980/175 |
| Ficarra et al. (40) | 2002 TNM | Gleason score | 67/28 | 187/40 | 26/69 | 112/115 | 21/74 | 177/50 |

NA, data not applicable; PSMs, positive surgical margins; NSMs, negative surgical margins; GS, Gleason Score; ISUP, International Society of Urologic Pathology (ISUP) system.

### FIGURE 2 | Forest plot for the association between pathological GS and PSMs risk.
Meta-Analysis
The pooled results from the included studies indicated that PSMs were associated with pathological GS (<6≥7) (RE model, pooled OR = 2.49; 95% CI: 2.19–2.83; P < 0.001, Figure 2), pathological stage (<T2≥T3) (RE model, pooled OR = 3.90; 95% CI: 3.18–4.79; P < 0.001, Figure 3), biopsy GS (<6≥7) (RE model, pooled OR = 1.53; 95% CI: 1.31–1.79; P < 0.001, Figure 4), p-PSA (FE model, pooled SMD = 0.37; 95% CI: 0.31–0.43; P < 0.001, Figure 5A), positive lymph node (PLN) (RE model, pooled OR = 4.44; 95% CI: 3.25–6.09; P < 0.001, Figure 5B), extraprostatic extension (EPE) (RE model, pooled OR = 4.44; 95% CI: 3.25–6.09; P < 0.001, Figure 5C), and seminal vesicle invasion (SVI) (RE model, pooled OR = 4.19; 95% CI: 2.87–6.13; P < 0.001, Figure 5D).

The results of meta-analysis of PSMs showed that no significant associations were found between PSMs and age (RE model, pooled SMD = 0.01; 95% CI: −0.07–0.10; P = 0.735, Figure 6A), nerve sparing (RE model, pooled OR = 0.90; 95% CI: 0.71–1.14; P = 0.388, Figure 6B), body mass index (BMI) (RE model, pooled SMD = 0.12; 95% CI: −0.05–0.30; P = 0.162, Figure 6C), and prostate volume (RE model, pooled SMD = −0.28; 95% CI: −0.62–0.05; P = 0.097, Figure 6D).

Subgroup Analysis
Considering that there was no significant heterogeneity in p-PSA and the number of studies that evaluated BMI, SVI, and prostate volume was relatively small, we only conducted subgroup analysis for biopsy GS, pathological GS, pathological stage, PLN, EPE, age, and nerve sparing (Table 3). Subgroup analyses were conducted according to the geographical region (Asian vs. non-Asian), year of publication (≥2014 vs. <2014), number of patients (≥1,000 vs. <1,000), and median follow-up (≥70 months vs. <70 months). The results of subgroup analysis were roughly the same as overall results. Besides, the heterogeneity decreased significantly in some subgroup analyses, such as geographical region in Asian, year of publication <2014, and number of patients <1,000 cases.

Sensitivity Analysis
To validate the reliability of our results, sensitivity analysis was performed. As shown in Supplementary Figure S1, the combined ORs for biopsy GS ranged from 1.47 (95% CI: 1.25–1.72) to 1.58 (95% CI: 1.37–1.85) (Supplementary Figure S1A), the combined ORs for pathological GS ranged from 2.39 (95% CI: 2.04–2.80) to 2.96 (95% CI: 2.59–3.39) (Supplementary Figure S1B), and the combined ORs for pathological stage ranged from 2.82 (95% CI: 2.46–3.23) to 3.22 (95% CI: 2.74–3.79) (Supplementary Figure S1C).
CI: 2.14–2.67) to 2.56 (95% CI: 2.26–2.90) (Supplementary Figure S1B), the combined ORs for pathological stage ranged from 3.73 (95% CI: 3.04–4.58) to 4.15 (95% CI: 3.47–4.96) (Supplementary Figure S1C), the combined ORs for PLN ranged from 2.88 (95% CI: 2.08–4.00) to 3.51 (95% CI: 2.67–4.79) (Supplementary Figure S1D), the combined ORs for nerve sparing ranged from 0.83 (95% CI: 0.66–1.04) to 0.97 (95% CI: 0.74–1.27) (Supplementary Figure S1E), and the combined ORs for EPE ranged from 3.84 (95% CI: 3.05–4.85) to 4.68 (95% CI: 3.36–6.53) (Supplementary Figure S1F). The pooled SMD for p-PSA ranged from 0.36 (95% CI: 0.29–0.42) to 0.44 (95% CI: 0.35–0.54) (Supplementary Figure S2A), and the pooled SMD for age ranged from −0.01 (95% CI: −0.09–0.07) to 0.03 (95% CI: −0.05–0.12) (Supplementary Figure S2B). These data suggested that the results were statistically robust. Because the number of included studies for BMI, EPE, SVI, and prostate volume was small, the sensitivity analysis was not valuable.

Publication Bias
The shape of funnel plots did not reveal any evidence of asymmetry (Figure 7). The statistical results of Egger’s test still did not show any publication bias for biopsy GS (p- Egger = 0.277, Figure 7A), pathological GS (p- Egger = 0.945, Figure 7B), pathological stage (p- Egger = 0.830, Figure 7C), PLN (p- Egger = 0.605, Figure 7D), EPE (p- Egger = 0.513, Figure 7E), SVI (p- Egger = 0.797, Figure 7F), age (p- Egger = 0.431, Figure 7G), and nerve sparing (p- Egger = 0.197, Figure 7H). However, a minimal publication bias existed in p-PSA (p- Egger = 0.047). As the number of studies on prostate volume and BMI was limited, the publication bias was not assessed.

DISCUSSION
PSMs are unfavorable pathological features, which suggest incomplete tumor resection and confer poorer cancer control after RP (38). It was reported that PSMs were present in 11–38% of patients treated by RP and patients with PSMs have a higher risk of BCR compared to those with negative surgical margins (NSMs) (41). A multi-institutional review in 2009 conducted by Yossepowitch et al. (42) concluded that PSMs in RP specimens may be considered as an adverse outcome following RP. Consistent with these findings, our recent studies (6, 7) demonstrated the adverse effect of PSMs on both BCR and cancer-specific survival through a systematic review and meta-analysis. However, not all patients with PSMs have poor tumor outcomes, and some patients with localized PCa will show tumor progression even in the no-PSMs cases.

PSMs are factors that may be modified by the surgical technique. It seems that surgeon’s experience plays an important role in the decrease in the incidence of PSMs (43). Considerable efforts have been devoted to identifying factors,
FIGURE 5 | Forest plots of studies evaluating the prognostic factors for p-PSA (A), PLN (B), EPE (C), and SVI (D) with PSMs risk.
FIGURE 6 | Forest plots of studies evaluating the association of PSMs and clinicopathological features in PCa patients. Age (A), nerve sparing (B), BMI (C), and prostate volume (D).
| Analysis specification | No. of studies | Study heterogeneity | Effects model | Pooled OR/SMD (95% CI) | P-Value |
|------------------------|---------------|---------------------|---------------|------------------------|---------|
| **BMI**                |               |                     |               |                        |         |
| Overall                | 3             | 83.2                | Random        | 0.12 (~0.05,0.30)      | 0.162   |
| p-PSA                  | 7             | 19.2                | Fixed         | 0.37 (~0.31,0.43)      | <0.001  |
| SVI                    | 4             | 74.8                | Random        | 4.19 (~2.87,6.13)      | <0.001  |
| **Prostate volume**    |               |                     |               |                        |         |
| Overall                | 3             | 76.3                | Random        | ~0.28 (~0.62,0.05)     | 0.097   |
| Age                    | 9             | 57                  | Random        | 0.01 (~0.07,0.10)      | 0.735   |
| Geographical region    |               |                     |               |                        |         |
| Asian                  | 5             | 49.6                | Random        | ~0.03 (~0.17,0.12)     | 0.724   |
| non-Asian              | 4             | 36.4                | Fixed         | 0.06 (~0.02,0.14)      | 0.149   |
| Year of publication    |               |                     |               |                        |         |
| ≥2014                  | 5             | 75.6                | Random        | ~0.01 (~0.12,0.11)     | 0.916   |
| <2014                  | 4             | 0                   | Fixed         | 0.02 (~0.09,0.14)      | 0.675   |
| No. of patients        |               |                     |               |                        |         |
| ≥1,000                 | 3             | 78.4                | Random        | 0.05 (~0.07,0.16)      | 0.442   |
| <1,000                 | 6             | 34.0                | Fixed         | ~0.02 (~0.14,0.10)     | 0.719   |
| **Biopsy GS (<6/>=7)** | 14            | 71.5                | Random        | 1.53 (1.31,1.79)       | <0.001  |
| Geographical region    |               |                     |               |                        |         |
| Asian                  | 4             | 28.2                | Fixed         | 1.19 (0.90,1.58)       | 0.277   |
| non-Asian              | 10            | 64.1                | Random        | 1.65 (1.42,1.93)       | <0.001  |
| Year of publication    |               |                     |               |                        |         |
| ≥2014                  | 9             | 64.8                | Random        | 1.44 (1.17,1.76)       | <0.001  |
| <2014                  | 5             | 41.1                | Fixed         | 1.75 (1.44,2.11)       | <0.001  |
| No. of patients        |               |                     |               |                        |         |
| ≥1,000                 | 5             | 50.2                | Random        | 1.84 (1.40,2.42)       | <0.001  |
| <1,000                 | 10            | 78.5                | Random        | 1.39 (1.13,1.70)       | 0.001   |
| Median follow-up       |               |                     |               |                        |         |
| ≥70 months             | 3             | 29.9                | Fixed         | 1.58 (1.32,1.90)       | <0.001  |
| <70 months             | 6             | 68.1                | Random        | 1.67 (1.13,2.46)       | 0.010   |
| **P-GS (<6/>=7)**      | 22            | 75.1                | Random        | 2.49 (1.92,2.83)       | <0.001  |
| Geographical region    |               |                     |               |                        |         |
| Asian                  | 4             | 0                   | Fixed         | 2.47 (2.04,2.99)       | <0.001  |
| non-Asian              | 18            | 79.2                | Random        | 2.48 (2.14,2.89)       | <0.001  |
| Year of publication    |               |                     |               |                        |         |
| ≥2014                  | 9             | 74.3                | Random        | 2.37 (1.90,2.96)       | <0.001  |
| <2014                  | 12            | 73.3                | Random        | 2.48 (2.08,2.95)       | <0.001  |
| No. of patients        |               |                     |               |                        |         |
| ≥1,000                 | 10            | 77.4                | Random        | 2.49 (2.02,2.87)       | <0.001  |
| <1,000                 | 12            | 73.5                | Random        | 2.48 (2.08,2.95)       | <0.001  |
| Median follow-up       |               |                     |               |                        |         |
| ≥70 months             | 8             | 66.2                | Random        | 2.04 (1.74,2.39)       | <0.001  |
| <70 months             | 9             | 76.6                | Random        | 2.87 (2.27,3.62)       | <0.001  |
| **Stage (<T2/>=T3)**   | 23            | 91.4                | Random        | 3.90 (3.18,4.79)       | <0.001  |
| Geographical region    |               |                     |               |                        |         |
| Asian                  | 6             | 0                   | Fixed         | 3.32 (2.75,4.00)       | <0.001  |
| non-Asian              | 17            | 93.9                | Random        | 4.06 (3.19,5.22)       | <0.001  |
| Year of publication    |               |                     |               |                        |         |
| ≥2014                  | 11            | 94.8                | Random        | 3.28 (2.20,4.89)       | <0.001  |
| <2014                  | 12            | 82.5                | Random        | 4.53 (3.64,5.64)       | <0.001  |
| No. of patients        |               |                     |               |                        |         |
| ≥1,000                 | 10            | 94.3                | Random        | 3.58 (2.74,4.69)       | <0.001  |
| <1,000                 | 13            | 87.9                | Random        | 4.24 (2.88,6.25)       | <0.001  |
| Median follow-up       |               |                     |               |                        |         |
| ≥70 months             | 7             | 75.8                | Random        | 4.24 (3.42,5.26)       | <0.001  |
| <70 months             | 10            | 95.8                | Random        | 3.58 (2.20,5.82)       | <0.001  |
such as p-PSA (44), positive biopsy cores (10), and clinical stage (36), which can predict PSMs and clinical outcome following RP. The conclusion of several published studies indicated that several unfavorable pathological features may be associated with PSMs. However, inconsistent results have also been demonstrated in the published studies. Besides, for patients with adverse features of PSMs, prediction parameters that are currently available for PSMs may not reliable.

A retrospective study conducted by Boorjian et al. (37) found that increased p-PSA and BMI, higher pathological stage/GS, and greater tumor volume were significantly associated with the risk of PSMs. Likewise, Ficarra et al. (40) found an association between PSMs and biopsy GS, pathologic stage and GS, and EPE; however, no correlation was found between PSMs and p-PSA. Hashimoto et al. (29) found that only PSA density and prostate volume were independent predictors of PSMs after robot-assisted RP. Meanwhile, no correlation was found with p-PSA, biopsy GS, and PLN. The inconsistent results from the above studies may due to small sample size, single-center design, and inhomogeneous population.

To the best of our knowledge, none of the studies have systematically addressed the preoperative predictive factors for PSMs after RP. In the present study, we identified 27 studies involving 50,014 patients, and the rate of PSMs was 24.2%, which is comparable to that in previous reports. The meta-analysis showed that p-PSA, biopsy GS (<6/≥7), pathological GS (<6/≥7), pathological stage (<T2/≥T3), PLN, EPE, and SVI had a statistically significant association with PSMs. Moreover, the pooled OR/SMD of the results suggested that age, BMI, prostate volume, and nerve sparing were not independent prognostic factors for PSMs in patients after RP. Subgroup analyses revealed a similar result despite different geographical regions, publication years, sample sizes, and median follow-ups. Further, sensitivity analysis and publication bias test were also performed, and the overall results showed that our data were stable and reliable.

This is the first comprehensive study to investigate the pathological features of PSMs and predictive factors for PSMs in patients treated with RP. Subgroup analyses revealed a similar result despite different geographical regions, publication years, sample sizes, and median follow-ups. Further, sensitivity analysis and publication bias test were also performed, and the overall results showed that our data were stable and reliable.

Nevertheless, the present study has some limitations that should be acknowledged. First, all the studies were retrospectively performed, which made our research more susceptible to recall or
selection bias. Second, a substantial heterogeneity was detected, while sensitivity analysis and subgroup analysis failed to identify the potential heterogeneity. Third, this study was limited to articles published in English and Chinese, which might have contributed to selection bias. As known, articles with positive results are more likely to be published. Therefore, this article also had a certain publication bias. Fourth, the number of included studies was limited in terms of publication bias and subgroup and sensitivity analyses, which could have led to unpersuasive conclusions. Therefore, more studies are required, which can provide more detailed individual high-quality data.

CONCLUSION

The meta-analysis demonstrates that p-PSA, biopsy GS, pathological GS, pathological stage, PLN, EPE, and SVI were independent factors predicting PSMs after RP, and a combination of these factors might be useful for predicting PSMs in PCa patients undergoing RP. Considering the limitations of the present analysis, it is necessary to conduct more large-scale and well-designed studies to validate our results in the future.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/Supplementary Material.

AUTHOR CONTRIBUTIONS

LZ conceptualized the study. BW, ZZ, and JY performed the literature search. HZ and YF analyzed the data. HZ wrote the original draft. LZ wrote, reviewed, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.539592/full#supplementary-material

Supplementary Figure 1 | Sensitivity analysis (pooled ORs) of the association between the predictive factors and PSMs risk. (A) biopsy GS; (B) pathological GS; (C) pathological stage; (D) PLN, and (E) nerve sparing.

Supplementary Figure 2 | Sensitivity analysis (pooled SMDs) of the association between the predictive factors and PSMs risk. (A) p-PSA; (B) age.
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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