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ORIGINAL RESEARCH

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Comparisons of cancer-specific and overall mortality in patients with biopsy- and TURP-diagnosed prostate cancer: a population-based propensity score-matching study

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Abstract

This population-based propensity score-matching study aimed to investigate the survival outcomes of patients with biopsy- and transurethral resection of the prostate (TURP)-diagnosed prostate cancer (PC). We obtained data from the Surveillance, Epidemiology and End Results (SEER) database, PC patients diagnosed by biopsy and TURP from 1975 to 2019 were enrolled. Cohort data were baseline-matched using a propensity score-matching (PSM) study. Compared with biopsy-confirmed PC (BPC) patients, prostate cancer-specific mortality (CSM) and overall mortality (OM) in patients with transurethral resection of the prostate (TURP)-diagnosed PC (TPC) were analyzed. A total of 26,027 cases were obtained for this study, of which 4770 cases (18.3%) were TPC patients and 21,257 cases (81.7%) were BPC patients. The proportion of TPC patients showed an increasing trend. The prognosis of TPC patients seemed worse, the ratios of CSM and OM were higher, and the median survival time was shorter (all $p < 0.05$). After PSM, TPC patients still had a worse prognosis. Compared with BPC patients, TPC patients' CSM and OM risks increased by 42.0% and 43.0%, respectively ($p < 0.001$). The results of subgroup analysis indicated earlier the stage of TPC patients, the higher the risk of OM, while systemic treatment after surgery may bring declines of CSM and OM (all p for interaction < 0.001). To our knowledge, we first used a large sample size to find that clinically suspected PC patients with obstruction, directly TURP will increase the risk of CSM and OM.

Keywords

Prostate cancer; Biopsy; TURP; Cancer-specific mortality; Overall mortality; Propensity score-matching study

1. Introduction

Current guidelines recommend needle biopsy for patients with suspected prostate cancer (PC) to confirm diagnosis and guide treatment [1, 2]. However, there are many cases of biopsy false negative diagnoses [1, 3]. Thus, transurethral resection of the prostate (TURP) may improve symptoms and help diagnose or exclude PC, especially for those with bladder outlet obstruction. Although the likelihood of diagnosing PC after TURP was low in patients with previously negative biopsies, TRUP may be considered a treatment option for patients with obstructive symptoms [1, 4]. As TURP is one of the best options for obstruction caused by prostatic hyperplasia [5]. Indeed, in patients receiving TURP without prior biopsy diagnosis, the incidence of incidental PC (iPC) is very low, approximately 8% [6]. There is usually no apparent clinical evidence of PC before TURP [7]. There are very few reports on survival outcomes of TURP-diagnosed PC. This question was answered in a recent retrospective Danish study; they included 64,059 patients with TURP, 63,781 with a final diagnosis of PC, 42,558 of whom were not screened for biopsy; they found that these patients with TPC had a shallow risk of prostate cancer-specific mortality (CSM), the 15-year cumulative incidence was 1.4% for all patients and 0.8% for patients with prostate-specific antigen (PSA) levels $<$10 ng/mL [8]. While their study only analyzed the survival rates of patients with a PSA of 25ng/mL and below; they also did not analyze the interval between the time of TURP and the time of diagnosis of PC, as well as did not separately analyze the prognosis of patients who underwent TURP without biopsy screening. Therefore, for patients with clinical suspicion of PC without biopsy, especially those with higher PSA, the survival prognosis of these TPC patients remains unknown and is worth further study [1, 2, 9].

It should be emphasized that these patients in our study differed from patients with iPC or established PC accompanied

by bladder outlet obstruction; the late was common during clinical practice [10]. For the latter population, TURP could bring symptom relief and PSA benefits [1, 11, 12]. Nevertheless, TURP may increase the risk of death for these patients [13, 14]. Although TURP for PC diagnostic purposes is not currently recommended [1], however, for patients without biopsy, TURP to relieve obstruction is permitted [4]. Many patients suspected of PC without biopsy directly undergo TURP because of bladder outlet obstruction in real-world clinical practice [8, 15]. This study intended to compare CSM and overall mortality (OM) of BPC patients, to analyze the risks of mortalities in TPC patients without biopsy screening, and to guide future Clinical practice.

2. Method

2.1 Data collection

We obtained access to the Surveillance, Epidemiology and End Results (SEER) database and included data on patients with biopsy-confirmed PC (BPC) and TURP-diagnosed PC (TPC) from 1975 to 2019. We excluded the data according to the following exclusion criteria: (a) insufficient survival time or survival time less than one month (with a unit of months, months = mo.); (b) cases with CSM unavailable; (c) age >90 years; (d) no clinical Gleason score (GS) confirmed by prostate biopsy. The items included in the study were age (with a unit of years old, years old = ys.), race, marital status (partner), house annual income (income), home location (home), diagnosis year, PSA, cases with TPC or BPC, pathological GS, summary stage according to SEER database 2004 (stage), time from PC diagnosed to subsequent treatment (time to treat) (with a unit of months, months = mo.), cancer-directed surgery (CDS), lymph nodes removal, radiation therapy (radiation), chemotherapy, systemic therapy, CSM, OM and survival time. We defined dead in CSM as PC-specific death and patients alive or other causes of death were excluded; OM was defined as patient death with any of the causes. We promise that all data will be appropriately handled, kept by a dedicated person, and used only for this research.

2.2 Statistical analysis

We used SPSS statistical software (v.27.0, IBM SPSS Statistics, Armonk, NY, USA) to conduct two independent samples Mann Whitney U Test, to compare the parameters before and after propensity score matching (PSM). Continuous variables were expressed as median and Mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. We used PSM to perform consistent matching of pre-treatment parameters. The specific parameters were age, partner, income, home, diagnosis year, PSA and stage as matching factors. The matching tolerance of PSM was 0.002, 1:1 ratio matching was adopted, and exact matching was preferred. The Multivariable Cox proportional hazard model was performed. The hazard ratio (HR) and 95% confidence intervals (CI) of the CSM and OM of the TPC relative to the BPC were calculated. Two adjusted models were analyzed: model 1 (adjusting for age, race, stage and PSA) and model 2 (adjusting for age, race, stage, PSA, pathological GS, CDS and systemic therapy). Subgroup analysis was then performed on the subgroups of age, race, partner, income, home, diagnosis year, stage, CDS and systemic therapy; their HR and 95% CI for CSM and OM, and p for interactions were calculated. The R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) software performed Kaplan-Meier analysis. Statistical difference was considered at $p < 0.05$.

3. Results

3.1 General information and frequency tendencies of TPC and BPC

We had a total of 453,988 cases but finally included a total of 26,027 cases in this study according to the inclusive and exclusive criteria (more than 420,000 cases were excluded, which might primarily be due to they did not have a clinical GS that was evaluated by prostate biopsy. All of the cases were diagnosed from 2010 to 2019. Of these, 4770 cases (18.3%) were TPC patients, while 21,257 (81.7%) were BPC patients. We found that over time TPC patients increased from 6.7% (2010) to a maximum of 13.0% (2018), showing an increasing trend year by year, while BPC patients, proportion first decreased from 10.3% (2010) to a minimum of 8.1% (2014), and then rose to a maximum of 11.3% (2018) (Fig. 1A). We then included a total of 24,371 cases to evaluate the propensity for RP that varied over the years, of which 4263 cases were offered radical prostatectomy (RP) and 20,108 cases without RP (1656 cases were excluded as it was unknown whether they accepted RP or not in the database). Then, we found the proportions of patients with RP or not RP were similar to those of BPC patients, both of which first decreased and then increased, respectively (Fig. 1B).

3.2 Comparisons of baselines and survival rates between TPC and BPC patients before PSM

Compared with BPC patients, TPC patients had a higher median age (73.0 ys *vs.* 68.0 ys), showing ethnic differences; they had more percentages of single (36.8% *vs.* 18.1%) but better economic status (income ≥$70,000, 52.6% *vs.* 48.0%), closer of diagnosis year (2014–2019, 59.7% *vs.* 52.2%), more proportion of pathological GS 6 and below (18.1% *vs.* 2.8%); but a higher proportion of PSA 98.0 ng/mL or more significant (56.9% *vs.* 19.4%), a higher proportion of distant metastasis (61.1% *vs.* 14.6%), more proportion of four or more lymph node removal (21.4% *vs.* 6.0%), more percentages of beam radiotherapy (15.4% *vs.* 12.3%), more percentages of chemotherapy (9.5% *vs.* 3.1%), and more postoperative systemic therapy (7.0% *vs.* 3.2 %) (all $p < 0.05$) (Table 1). Even having a shorter median time from time to treatment (0 mo. *vs.* 1 mo.), TPC patients had significantly worse prognosis; they had higher rates of CSM (Fig. 2A) and OM (Fig. 2B) and shorter median survival time (19.0 mo. *vs.* 42.0 mo.) (all $p < 0.001$).

Comparisons of baselines and survival rates between TPC and BPC patients after PSM.

After PSM, we obtained equal case numbers of TPC (n = 2348) and BPC (n = 2348) patients. There were no significant

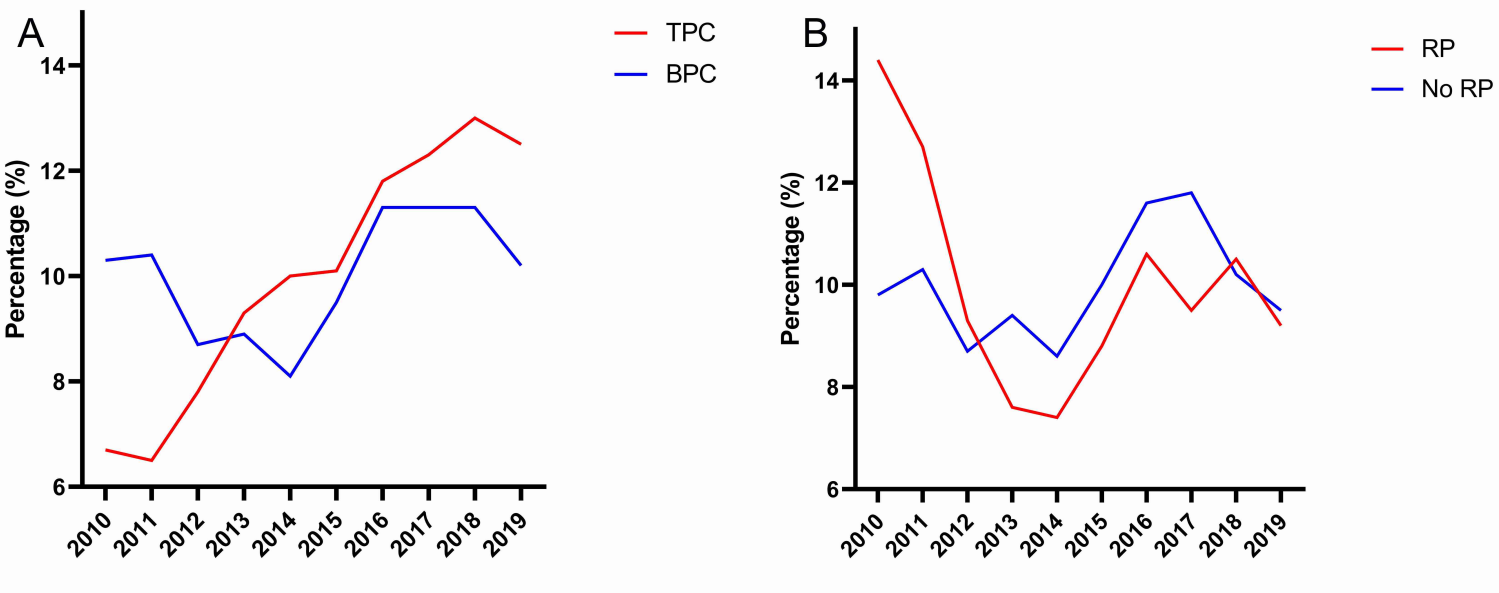

FIGURE 1. Frequency tendencies from 2010 to 2019 from the SEER database. (A) Frequency tendencies of TPC (n = 4770) and BPC (n = 21,257); (B) Frequency tendencies of RP (n = 4263) and No RP (n = 20,108). SEER: Surveillance, Epidemiology, and End Results; TPC: prostate cancer diagnosed by transurethral resection of the prostate; BPC: prostate cancer diagnosed by prostate biopsy; RP: radical prostatectomy; No RP: no radical prostatectomy.

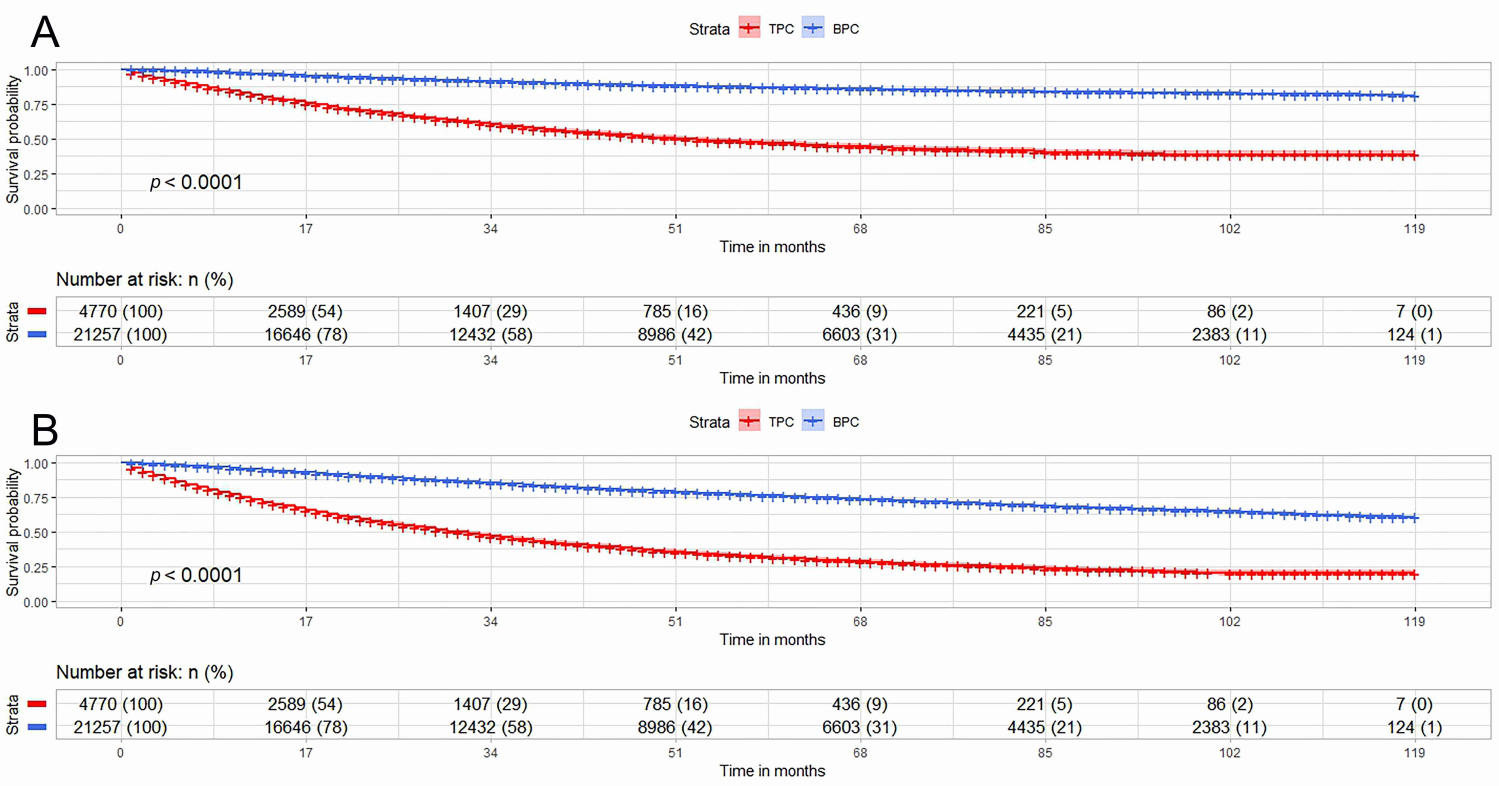

FIGURE 2. Survival rates between TPC and BPC patients before PSM. (A) CSM comparison between TPC and BPC patients; (B) OM comparison between TPC and BPC patients. TPC: prostate cancer diagnosed by transurethral resection of the prostate; BPC: prostate cancer diagnosed by prostate biopsy; PSM: propensity score matching; CSM: prostate cancer-specific mortality; OM: overall mortality.

TABLE 1. Comparisons between BPC and TPC before PSM.

Variables	TPC (n = 4770)	BPC (n = 21,257)	*p* value#
Age (ys.)			
Median (IQR)	73.0 (64.0–81.0)	68.0 (62.0–75.0)	<0.001
Mean ± SD	72.40 ± 10.48	68.38 ± 9.48	
Race N (%)			
White	3648 (76.5)	15,982 (75.2)	0.03
Black	654 (13.7)	2705 (12.7)	
Others	417 (8.7)	1612 (7.6)	
Unknown/Missing value	51 (1.1)	958 (4.5)	
Partner N (%)			
Married	2654 (55.6)	9601 (45.2)	<0.001
Single	1754 (36.8)	3844 (18.1)	
Unknown/Missing value	362 (7.6)	7812 (36.8)	
Income N (%)			
<$70,000	2261 (47.4)	11,049 (52.0)	<0.001
≥$70,000	2508 (52.6)	10,195 (48.0)	
Missing value	1 (0.0)	13 (0.1)	
Home N (%)			
Big city	2495 (52.3)	10,999 (51.7)	0.47
Small city	2274 (47.7)	10,245 (48.2)	
Missing value	1 (0.0)	13 (0.1)	
Diagnosis year			
2010–2014	1923 (40.3)	10,153 (47.8)	<0.001
2015–2019	2847 (59.7)	11,104 (52.2)	
Pathological GS N (%)			
≤6	865 (18.1)	595 (2.8)	<0.001
=7	391 (8.2)	1937 (9.1)	
8–10	57 (1.2)	418 (2.0)	
No RP	3364 (70.5)	16,744 (78.8)	
Unknown	93 (1.9)	1563 (7.4)	
PSA (ng/mL) N (%)			
0.1 or less	18 (0.4)	69 (0.3)	<0.001
Test, results not in the chart	114 (2.4)	4965 (23.4)	
98.0 ng/mL or greater	2714 (56.9)	4119 (19.4)	
Unknown/Missing value	1924 (40.3)	12,104 (56.9)	
Stage N (%)			
Localized	1363 (28.6)	15,418 (72.5)	<0.001
Regional	241 (5.1)	1621 (7.6)	
Distant	2915 (61.1)	3094 (14.6)	
Unknown/unstaged	251 (5.3)	1124 (5.3)	
Time to treat (mo.)			
IQR	0 (0–1)	1.00 (0.00–2.00)	<0.001
Range	0–23	0–24	
Missing value	683 (14.3)	9314 (43.9)	

TABLE 1. Continued.

Variables	TPC (n = 4770)	BPC (n = 21,257)	*p* value#
CDS N (%)			
Yes	1434 (30.1)	6416 (30.2)	
No	3258 (68.3)	13,645 (64.2)	0.06
Unknown	78 (1.6)	1196 (5.6)	
Lymph nodes removal N (%)			
1 to 3 removed	81 (1.7)	625 (2.9)	
4 or more removed	1023 (21.4)	1273 (6.0)	<0.001
Biopsy only	127 (2.7)	44 (0.2)	
Unknown or missing	3539 (74.2)	19,315 (90.9)	
Radiation			
Beam	736 (15.4)	2618 (12.3)	
Others	12 (0.3)	623 (2.9)	<0.001
Unknown or missing	4022 (84.3)	18,016 (84.8)	
Chemotherapy			
Yes	454 (9.5)	657 (3.1)	<0.001
No or unknown	4316 (90.5)	20,600 (96.9)	
Systemic therapy			
Before surgery	58 (1.2)	260 (1.2)	
After surgery	332 (7.0)	683 (3.2)	<0.001
No or unknown	4380 (91.8)	20,314 (95.6)	
CSM N (%)			
Dead	1739 (36.5)	2263 (10.6)	<0.001
Alive or other death	3031 (63.5)	18,994 (89.4)	
OM N (%)			
Dead	2661 (55.8)	4658 (21.9)	<0.001
Alive	2109 (44.2)	16,599 (78.1)	
Survival time (mo.)			
IQR	19.0 (8.0–38.3)	42.0 (19.0–78.0)	
Range	1.0–119.0	1.0–119.0	<0.001
Mean ± SD	26.98 ± 25.61	49.08 ± 34.61	

TPC: TURP-diagnosed PC; BPC: biopsy-confirmed PC; GS: Gleason score; No RP: no radical prostatectomy; CDS: cancer-directed surgery; CSM: cancer-specific mortality; OM: overall mortality; PSA: Prostate-specific antigen; IQR: interquartile range; SD: standard deviation; N: number. # Mann Whitney U Test.

differences in age, race, partner, income, home, diagnosis year, PSA, stage, chemotherapy and systemic treatment between the two cohort cases (all $p > 0.05$) (Table 2). However, compared with BPC patients, although TPC patients had a shorter median time from diagnosis to treatment (0 mo. *vs.*1 mo.) and more percentage of beam radiotherapy (25.0% *vs.* 18.0%), while they had a lower rate of CDS (2.9% *vs.* 11.4%) and higher proportions of CSM (49.5% *vs.* 42.3%) (Fig. 3A) and OM (62.3% *vs.* 53.0%) (Fig. 3B), and shorter median survival time (18.0 mo. *vs.* 22.0 mo.) (all $p < 0.001$).

3.3 TPC patients had a higher risk of mortality

No matter whether it was before or after PSM, whether or not in adjusted model 1 or model 2 for mortality risk evaluation, our further analysis showed that TPC patients had significantly higher risks of CSM and OM (all $p < 0.001$) (Table 3). Taking adjusted model 2 as an example, the risks of CSM and OM in TPC patients were much higher, with HR = 1.42 (95% CI 1.30–1.56) and HR = 1.43 (95% CI 1.32–1.55), respectively. The risks of CSM and OM increased in TPC patients by 42.0% and 43.0%, respectively, compared with those of BPC patients.

TABLE 2. Comparisons between BPC and TPC after PSM.

Variables	TPC (n = 2348)	BPC (n = 2348)	*p* value#
Age (ys.)			
Median (IQR)	72.0 (63.0–80.0)	71.00 (64.0–79.0)	0.55
Mean ± SD	71.43 ± 10.34	71.25 ± 10.10	
Race N (%)			
White	1685 (71.8)	1690 (72.0)	0.94
Black	433 (18.4)	406 (17.3)	
Others	225 (9.6)	239 (10.2)	
Unknown/Missing value	5 (0.2)	13 (0.6)	
Partner N (%)			
Married	1216 (51.8)	1218 (51.9)	0.27
Single	1001 (42.6)	914 (38.9)	
Unknown/Missing value	131 (5.6)	216 (9.2)	
Income N (%)			
<$70,000	1120 (47.7)	1091 (46.5)	0.41
≥$70,000	1227 (52.3)	1257 (53.5)	
Missing value	1 (0.0)	/	
Home N (%)			
Big city	1257 (53.5)	1278 (54.4)	0.53
Small city	1090 (46.4)	1070 (45.6)	
Missing value	1 (0.0)	/	
Diagnosis year N (%)			
2010–2014	926 (39.4)	949 (40.4)	0.49
2015–2019	1422 (60.6)	1399 (59.6)	
Pathological GS N (%)			
≤6	27 (1.1)	3 (0.1)	0.83
=7	12 (0.5)	26 (1.1)	
8–10	4 (0.2)	12 (0.5)	
No RP	2300 (98.0)	2274 (96.8)	
Unknown	5 (0.2)	33 (1.4)	
PSA (ng/mL) N (%)			
0.1 or less	18 (0.8)	3 (0.1)	0.47
Test, results not in the chart	100 (4.3)	127 (5.4)	
98.0 ng/mL or greater	2230 (95.0)	2218 (94.5)	
Unknown/Missing value	/	/	
Stage N (%)			
Localized	101 (4.3)	88 (3.8)	0.92
Regional	88 (3.7)	103 (4.4)	
Distant	2159 (92.0)	2156 (91.8)	
Time to treat (mo.)			
IQR	0 (0–1)	0.00 (0.00–1.00)	<0.001
range	0–23	0–23	
Missing value	253 (10.8)	170 (7.2)	

TABLE 2. Continued.

Variables	TPC (n = 2348)	BPC (n = 2348)	*p* value#
CDS N (%)			
Yes	67 (2.9)	267 (11.4)	<0.001
No	2228 (94.9)	2026 (86.3)	
Unknown	53 (2.3)	55 (2.3)	
Lymph nodes removal N (%)			
1 to 3 removed	15 (0.6)	5 (0.2)	<0.001
4 or more removed	27 (1.1)	23 (1.0)	
Biopsy only	105 (4.5)	16 (0.7)	
Unknown or missing	2248 (93.7)	2304 (98.1)	
Radiation			
Beam	587 (25.0)	423 (18.0)	<0.001
Others	7 (0.3)	15 (0.6)	
Unknown or missing	1754 (74.7)	1910 (81.3)	
Chemotherapy			
Yes	373 (15.9)	401 (17.1)	0.27
No or unknown	1975 (84.1)	1947 (82.9)	
Systemic therapy			
Before surgery	49 (2.1)	86 (3.7)	0.23
After surgery	243 (10.3)	174 (7.4)	
No or unknown	2056 (87.6)	2088 (88.9)	
CSM N (%)			
Dead	1162 (49.5)	994 (42.3)	<0.001
Alive or other death	1186 (50.5)	1354 (57.7)	
OM N (%)			
Dead	1462 (62.3)	1245 (53.0)	<0.001
Alive	886 (37.7)	1103 (47.0)	
Survival time (mo.)			
IQR	18.0 (7.0–35.0)	22.0 (11.0–40.0)	<0.001
Range	1.0–119.0	1.0–119.0	
Mean ± SD	24.22 ± 22.09	28.79 ± 23.74	

TPC: TURP-diagnosed PC; BPC: biopsy-confirmed PC; GS: Gleason score; No RP: no radical prostatectomy; CDS: cancer-directed surgery; CSM: cancer-specific mortality; OM: overall mortality; PSA: Prostate-specific antigen; IQR: interquartile range; SD: standard deviation; N: number. # Mann Whitney U Test.

3.4 Subgroup analysis

We then performed a subgroup analysis to determine which subgroups of TPC patients may have a potential benefit in survival compared with BPC patients. We performed subgroup analysis on age, race, partner, income, home, diagnosis year, stage, CDS and systemic therapy. Except for post-operative systemic therapy, all other subgroups in BPC patients had better survival outcomes than TPC patients (Fig. 4). Compared with preoperative systemic therapy, TPC patients had better survival outcomes in CSM and OM than BPC patients (p for interaction < 0.001), suggesting that systemic therapy after RP brought survival benefits in patients with TPC. Compared with BPC patients, TPC patients with all different stages had worse survival outcomes, and the earlier the stage, the lower the risk of overall survival (p for interaction < 0.001), suggesting that for newly suspected PC patients, regardless of clinical stage, biopsy should be performed rather than TURP to confirm the diagnosis to reduce the overall risk of death. Recently diagnosed TPC cases (2015–2019) were at higher risk of CSM and OM than previously diagnosed cases (2010–2014) (p for interaction < 0.001), suggesting that newly suspected PC patients should also undergo a biopsy to confirm the diagnosis to reduce CSM and OM risk.

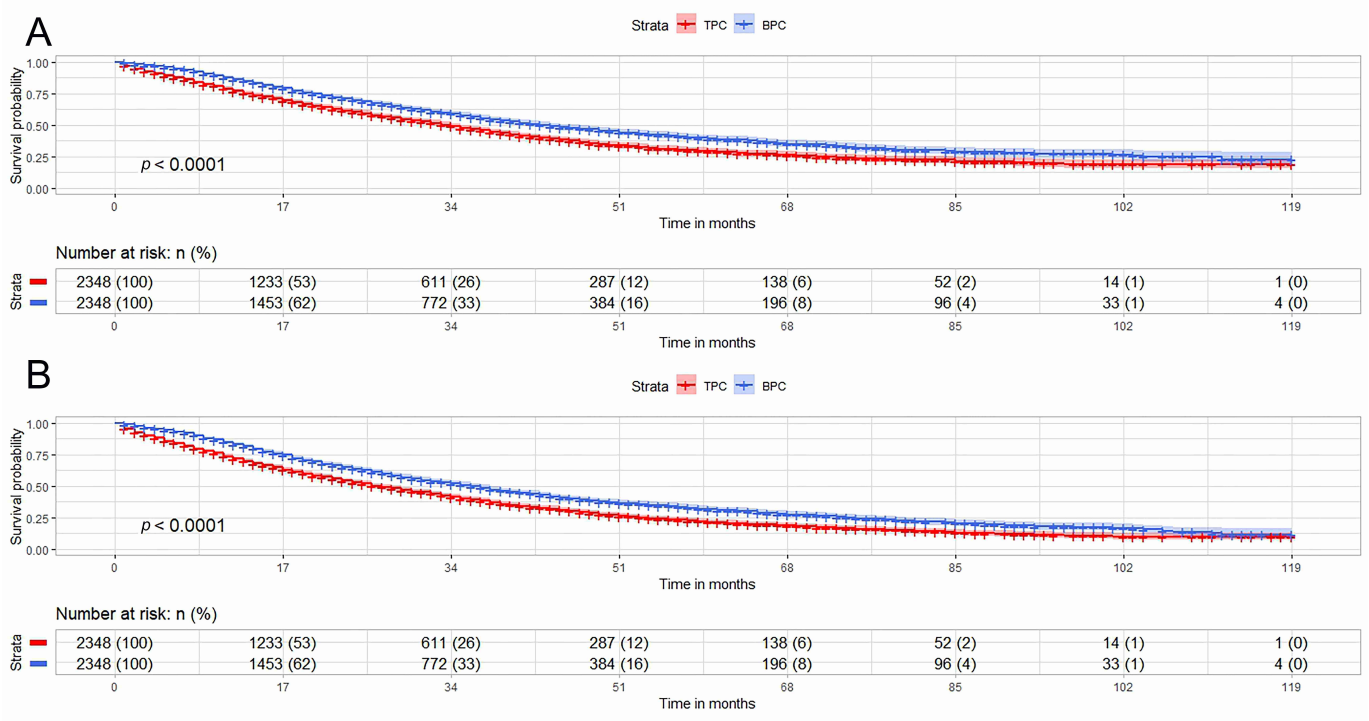

FIGURE 3. Survival rates between TPC and BPC patients after PSM. (A) CSM comparison between TPC and BPC patients; (B) OM comparison between TPC and BPC patients. TPC: prostate cancer diagnosed by transurethral resection of the prostate; BPC: prostate cancer diagnosed by prostate biopsy; PSM: propensity score matching; CSM: prostate cancer-specific mortality; OM: overall mortality.

TABLE 3. Multivariable Cox proportional hazard model for CSM and OM for TURP (n = 4770 before PSM, and n = 2348 after PSM) for unselected patients.

Outcomes	TPC HR (95% CI)	*p*-value
CSM		
Non-adjusted	5.57 (5.22–5.94)	$p < 0.001$
Adjusted model 1	1.35 (1.25–1.46)	$p < 0.001$
Adjusted model 2	1.39 (1.28–1.51)	$p < 0.001$
PSM Non-adjusted	1.38 (1.27–1.51)	$p < 0.001$
PSM Adjusted model 1	1.38 (1.27–1.51)	$p < 0.001$
PSM Adjusted model 2	1.42 (1.30–1.56)	$p < 0.001$
OM		
Non-adjusted	4.39 (4.19–4.62)	$p < 0.001$
Adjusted model 1	1.36 (1.27–1.46)	$p < 0.001$
Adjusted model 2	1.41 (1.31–1.51)	$p < 0.001$
PSM Non-adjusted	1.39 (1.29–1.50)	$p < 0.001$
PSM Adjusted model 1	1.39 (1.29–1.50)	$p < 0.001$
PSM Adjusted model 2	1.43 (1.32–1.55)	$p < 0.001$

Adjusted model 1 adjusts for age, race, stage and PSA.
Adjusted model 2 adjusts for age, race, stage, PSA, pathological GS, CDS and systemic therapy.
The PSM-non-adjusted model adjusts for none.
PSM-adjusted model 1 adjusts for age, race, stage and PSA.
PSM-adjusted model 2 adjusts for age, race, stage, PSA, pathological GS, CDS and systemic therapy.
TPC: TURP-diagnosed PC; HR: hazard ratio; CI: confidence intervals; CSM: cancer-specific mortality; OM: overall mortality; PSM: propensity score-matching.

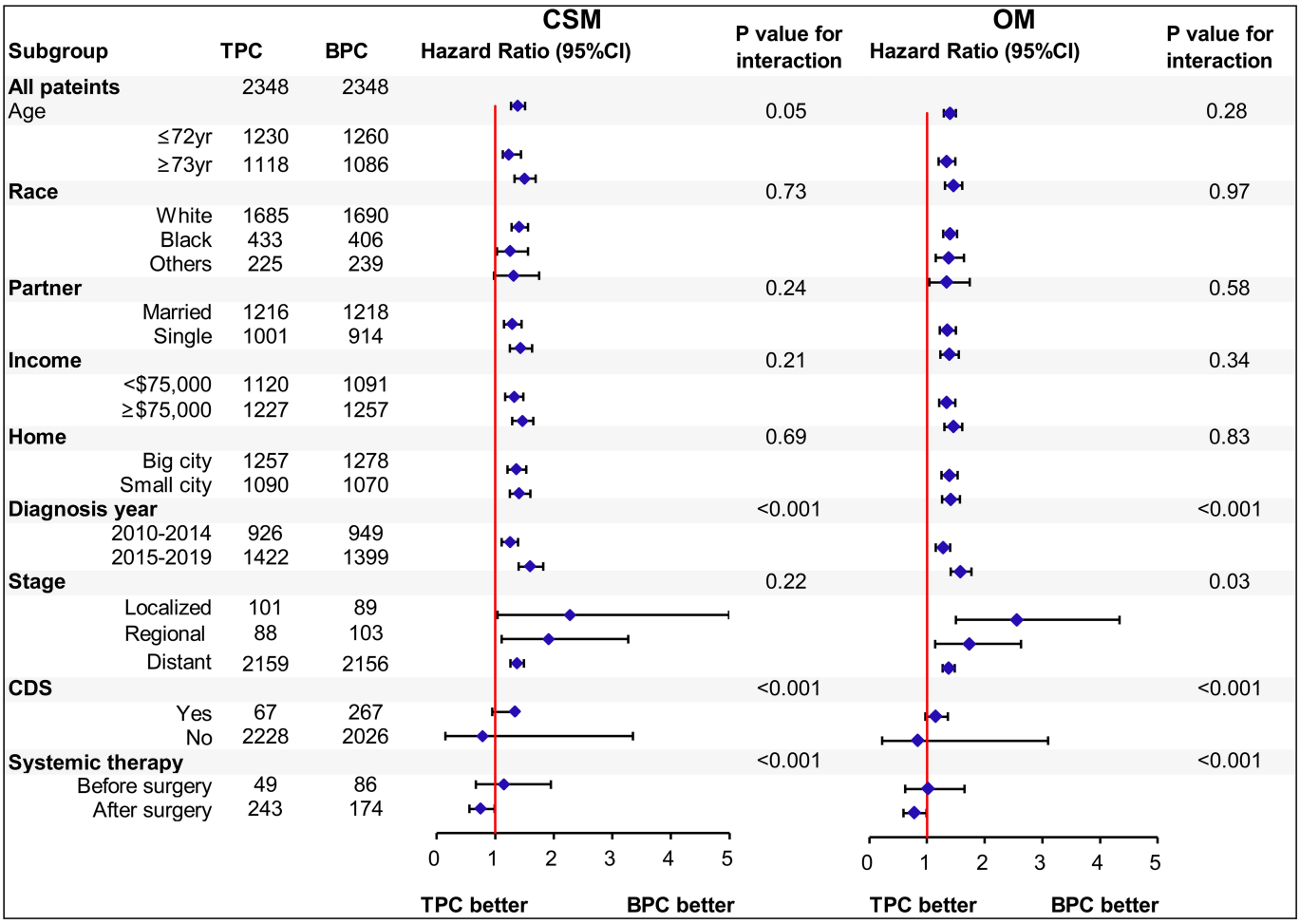

FIGURE 4. Subgroup analysis for TPC patients in survival benefit compared with BPC patients after PSM. Except for post-operative systemic therapy, all other subgroups of TPC patients had worse survival in CSM and OM compared with BPC patients. TPC: prostate cancer diagnosed by transurethral resection of the prostate; BPC: prostate cancer diagnosed by prostate biopsy; PSM: propensity score matching; CSM: prostate cancer-specific mortality; OM: overall mortality.

4. Discussion

Regarding patients with clinically suspicious PC without biopsy, the survival rate of patients diagnosed directly by TURP remained unclear before our study. Our study is different from previous studies, which focused on how to do negative results after initial biopsy, or iPC confirmed by TURP, or the outcomes of PC patients treated with TURP to improve symptoms. This study used population-based data to compare CSM and OM in patients with confirmed PC by TURP without initial biopsy. We found that TPC patients had significantly higher risks of CSM and OM than BPC patients.

For patients with negative biopsy, TURP could improve the symptoms of obstruction and increase the diagnosis of PC in a certain. A study found TURP helped screen for PC in patients with a previous negative biopsy but elevated PSA [16]. Moreover, TURP did not increase the risk of clinical PC in digital rectal examination-negative patients in the next 10 years [17]. However, direct TURP for diagnostic purposes is not recommended in patients with suspected PC who have not been screened by biopsy [1, 4]. Although it was not recommended, our results, actual clinical practice, and literature report all found that many suspected PC patients were still directly undergoing TURP for treatment and diagnosis purposes [8, 15]. Our study found that in the past decade, the number of patients diagnosed with TURP had increased yearly; its percentage was supposed to be more than 10%. In fact, for the diagnostic PC purpose, TURP was not superior to transrectal ultrasonography (TRUS)-guided prostate biopsy in patients with moderate lower urinary tract symptoms (LUTS) and PSA ≥4 ng/mL [15]. A recent retrospective study by Maria *et al.* [8] in Denmark was the first to report survival of patients with TURP-diagnosed PC in a large sample size; they included 63,781 TURP patients with a final diagnosis of PC, of whom 42,558 underwent TURP without initial biopsy, and found that these patients had a shallow risk of PC-specific death, with a 15-year cumulative incidence of 1.4% for all patients and 0.8% for patients with PSA levels <10 ng/mL. However, as mentioned above, they only studied the survival of patients with PSA of 25 ng/mL and below; and did not consider the interval between the time of TURP and the time of PC diagnosis. Furthermore, they did not separately analyze the prognosis of patients not screened by initial biopsy before TURP. Thus, their study was quite different from our study. In our study, the TPC patients generally had higher PSA and a higher proportion of distant metastasis. Among them, the

proportion of PSA 98.0 ng/mL or more significant was as high as 56.9%, and the distant metastasis reached 61.1%. Therefore, the TPC patients in our study had more advanced diseases. We found that for these patients, direct TURP for diagnosis of PC would significantly increase the risk of CSM and OM, increasing by 42.0% and 43.0%, respectively. And this risk of reduction in overall survival was found in TPC patients with all kinds of stages. Therefore, we emphasized that for new patients who have high clinical rates of PC, even if they may have obstructive symptoms, no matter what stages of PC may be, the biopsy should be performed to confirm the diagnosis, rather than TURP used to relieve symptoms, as well as to make diagnosis purpose.

TURP may help to exclude PC after or before the biopsy. A study found that the cumulative incidence of PC after benign TURP with PSA <10 ng/mL before TURP was low, only about 3% [8]. However, from the perspective of diagnosing PC, it appeared that TURP had a limited role. Accumulated evidence suggested TURP may be inferior to Holmium laser enucleation of the prostate (HoLEP) for diagnosing PC. In recent years, the application of HoLEP to male bladder outlet obstruction had received extensive attention; and has some advantages over TURP to a certain extent [18]. The studies found that HoLEP could provide significantly higher detection rates of iPC than bipolar TURP, which may be because HoLEP was more effective in removing more prostate tissue [19, 20]. While in patients with negative preoperative biopsy, patients confirmed PC after HoLEP was not uncommon (5.64%, 70/1240) [21]. For patients diagnosed with iPC after HoLEP, active surveillance was generally recommended for low- and intermediate-risk patients and high-risk patients may also experience symptomatic benefits. Still, systemic therapy was required [22]. Post-operative PSA after HoLEP was considered an independent predictor of future PC diagnosis; when PSA reached more than 1.73 ng/mL in the first year after HoLEP, rigorous follow-up and diagnostic investigation of PC was required [23]. Therefore, HoLEP may have more advantages than TURP in detecting PC in patients with less possibility of clinical PC after biopsy and complicated with obstruction. However, it was not yet known whether HoLEP affected the prognosis of PC patients. While positive tissue expression of PC-associated mRNA, obtained from TURP after negative biopsies, was found to be a promising marker for the presence of iPC in BPH patients [24]. In addition, cell cycle progression testing of TURP tissues was shown to be a significant independent prognostic factor for CSM in TRUP-treated PC patients [25]. In recent years, magnetic resonance imaging (MRI)-based biopsy technology has been widely used in diagnosing PC. In patients with MRI-visible lesions, MRI combined biopsy, targeted and systematic biopsy could improve the detection rate of PC [26]. Therefore, it may be unnecessary to perform TURP or HoLEP solely to diagnose PC; but they may be used to improve obstructive symptoms after a negative biopsy.

Many PC cases were offered TURP to improve bladder outlet obstruction. However, TURP was not conducive to survival benefits. A study based on SEER data found that 12,676 men with PC from 1992 to 2007 underwent at least one surgery for bladder outlet obstruction after PC treatment [10]. In another study based on SEER data, 36,003 patients with metastatic PC and bladder outlet obstruction from 2004 to 2016 were included; compared with PC patients with non-TURP (n = 33,180), increased OM and CSM in PC patients with TURP were found [13]. Similar to its conclusion observed in another SEER-based study. They included 9.3% of PC men (2742/29,361) who underwent TURP after diagnosis; and found that TURP was associated with a higher risk of local tumor progression and all-cause mortality when TURP performed within the first few months after needle biopsy [14]. These studies were significantly different from our study. The patients in our study were patients with undiagnosed PC. PC-related treatments, such as systemic or local therapy, should be performed for patients with confirmed PC before TURP. Although post-TURP, systemic therapy before RP may not confer a survival benefit. In addition, unlike TURP, PC patients offered local therapy, including RP and RT, had LUTS symptom relief and survival benefits [1, 27]. A study found similar survival benefits even in metastatic PC patients receiving local treatment [28]. Patients with relatively low tumor risk (predicted OM risk ≤20%) and good health performance appeared to benefit more [29]. In a systematic review, local treatment, including RP and radical radiation (RT) with or without androgen deprivation therapy (ADT), had advantages over ADT alone for overall survival and cancer-specific survival in clinically node-positive PC patients [30]. Therefore, local therapy may improve obstructive symptoms in patients with suspected PC and provide a survival benefit after biopsy-positive diagnosis. We further found that for patients with TPC, systemic therapy after RP brought survival benefits more than systemic therapy before RP, especially for those patients diagnosed with progressive or advanced PC postoperatively, which was consistent with current guidelines [32]. In addition to TURP, patients with confirmed PC may also undergo focal therapy. Focal therapy, as a treatment modality for eliminating local cancer tissue (including high-intensity focused ultrasound, cryotherapy, focal laser ablation, focal brachytherapy, *etc.*), in the treatment of PC also had specific effects, including PSA reduction, failure-free survival, recurrence-free survival and progression-free survival; however, whether it is decreasing CSM and OM was still inconclusive [31, 32]. In recent years, with new drugs, the update of treatment methods, and the close cooperation of multidisciplinary teams, survival was significantly improved for patients with localized or advanced PC [9, 32]. Nevertheless, a standardized diagnosis and treatment follow-up protocol will be needed to improve PC patient outcomes [33].

This study had some limitations. Firstly, it was a retrospective study that only covered part of the population from North America. Secondly, the TPC patients had high PSA and advanced stages; thus, our conclusions may only suit some patients with PC suspicious. Furthermore, we did not analyze by the tumor (T), node (N) and metastasis (M) stage or perform subgroup analyses of different PSA populations as a prominent absence of PSA records from SEER data. We also did not perform a subgroup analysis of the contribution of benign prostatic hyperplasia (BPH) to the risk of mortality in PC patients. However, studies have found that BPH may also increase the risk of PC mortality; even a study found it increased mortality

risk by 2–8 times [34]. In addition, 10-year PC mortality after TURP in BPH patients was 1.37 (0.81–2.29) [35], even though it was unclear whether the increased mortality was due to TURP or BPH. We estimated that most TPC patients treated with TURP were supposed to be associated with obstructive symptoms caused by BPH. Due to data limitations, although we could not make an adequate distinction, we may still draw our research conclusions, as TURP was performed almost because of obstruction, mainly caused by BPH, and TURP that was not aimed at diagnosing PC in clinical practice, which may be extremely rare for diagnosing PC.

5. Conclusions

To our knowledge, we found that TURP performance may increase the risk of CSM and OM for clinically suspected PC patients with obstruction without initial biopsy. Therefore, we emphasize that no matter what stage of PC may be considered clinically, for newly suspected PC patients with obstructive symptoms, a biopsy should be performed, and subsequent local therapy such as RP or RT rather than TURP may be considered as it could relieve symptoms and improve survival at the same time.

ABBREVIATIONS

HR: hazard ratio; PSM: propensity score matching (by 1:1 matching); CDS: Cancer-directed surgery; GS: Gleason Score; PSA: Prostate-specific antigen; stage: summary stage according to SEER database 2004; CI: confidence interval; CSM: cancer-specific survival; OM: overall survival.

AVAILABILITY OF DATA AND MATERIALS

The data can be accessed from the SEER database.

AUTHOR CONTRIBUTIONS

YBW—Conceptualization. RCZ, RCL, LL, TL, LFY and QGZ—Formal analysis and investigation. ZSC—Writing–original draft preparation. ZSC and YBW—Writing–review and editing. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was exempt from approval of Ethics Committee of Fujian Provincial Hospital or Fuding Hospital, considering that SEER data were de-identified and publicly available for research use.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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