Research Square

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Prognosis of men with high-risk prostate cancer stratified by risk factors: A population-based retrospective cohort study

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Research article

Keywords: prostate cancer; high-risk factors; prognosis; SEER.

Posted Date: April 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-23203/v1

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Version of Record: A version of this preprint was published at Translational Cancer Research on October 1st, 2020. See the published version at https://doi.org/10.21037/tcr-20-1578.

Abstract

Objective: To evaluate the prognosis of men with high-risk prostate cancers (PCa) stratified by high-risk factors.

Methods: Men with localized high-risk PCa were identified from 2004 to 2015. Kaplan–Meier analysis and Cox regressions were adopted to evaluate prostate cancer-specific survival (PCSS).

Results: A total of 151,799 patients were included. Seven risk groups were divided including one high-risk factor of T3-4 (A1), prostate-specific antigen (PSA) >20 ng/ml (A2), and Gleason score (GS) 8-10, two high-risk factors of T3-4 PSA>20 ng/ml (B1), T3-4 GS 8-10 (B2), PSA>20 ng/ml GS 8-10 (B3), and three high-risk factors of T3-4 PSA>20 ng/ml and GS 8-10 (C). The PCSS results showed that A1 was the best among all groups. A2, A3 and B1 were similar and were all better than B2. No significant difference existed between B3 and C and these two were the worst in prognosis. The 10-year PCSS rates of A1, A2, A3, B1, B2, B3, and C group were 95.8%, 86.9%, 86.1%, 86.9%, 80.8%, 64.7% and 65.6%, respectively. Three simplified groups were divided including a good prognosis group (A1), an intermediate prognosis group (A2, A3, B1 and B2), and a poor prognosis group (B3 and C). The 10-year PCSS rate of three groups were 95.8% vs 85.1% vs 66.5%. Compared to the good prognosis group, the HR of the intermediate and poor prognosis group were 4.21(3.96~4.48) and 11.36 (10.59~12.19). A nomogram was built based on these factors. The C-index of the nomogram was 0.772, indicating a good accuracy of the model.

Conclusions: We regrouped men with high-risk PCa according to their prognosis. PCa with three high-risk factors was not more aggressive than that with two of GS 8-10 and PSA >20 ng/ml.

1. Introduction

Prostate cancer (PCa) is the most common malignancy in the male genitourinary system, making up about 15% of all malignant tumors in the world [1, 2]. In 2019, it is estimated that there are 174,650 men newly diagnosed with PCa and 31,620 deaths of PCa in the United States [3]. In spite of increased screenings by prostate-specific antigen (PSA), a fair proportion of patients are still at high-risk stages [4]. Although many risk stratification schemes and nomograms have been reported recently [5, 6], the most commonly used stratification is still the one developed by D'Amico et al [7–9]. With the PSA concentration, Gleason score (GS) and tumor-node-metastasis (TNM) staging, the localized PCa is commonly classified into low-risk, intermediate-risk and high-risk groups. The high-risk group accounts for about 15% of prostate cancer diagnoses, and is characterized by recurrence and high cancer-related death. It is one of the important causes of death in PCa diseases [10].

Even though the prognosis of men with high-risk PCa has been evaluated in many studies, the survival results of patients with detailed high-risk factors of PCa have rarely been reported before. The prognosis of high-risk PCa varies greatly between different risk factors [11]. The 5-year biochemical recurrence (BCR) free survival for men assigned to the high-risk group by clinical T3a stage was 77.8%, by GS 53.7%, and by PSA level 41.0% [12]. Besides, the number of high-risk factors also seriously affect the prognosis of patients. Walz et al. [13] reported that men with one risk factor had a more favorable 5-year BCR-free survival (50.3%) than those with two or more risk factors (27.5%).

A nomogram is a convenient tool for predicting the probability of certain clinical events in an individual patient. It can also be useful for clinical risk stratification, decision-making and personalized treatment. The Surveillance, Epidemiology and End Results (SEER) program covers approximately 28% of all cancer cases of the US population. It incorporates patient demographics, tumor characteristics and treatment from population-based cancer registries.

The aim of this study was to analyze the prognosis of men with all possible high-risk PCa groups, and to construct a predictive model of nomograms to predict survival rates of men with high-risk PCa.

Materials And Methods

2.1 Data source

The data of this study were derived from the Surveillance, Epidemiology and End Results (SEER) database from January 1, 2004, to December 31, 2015. Men with primary localized (cT1-4N0M0) PCa were retrospectively identified with the software of SEER* STAT.

2.2 Inclusion and exclusion criteria

Patients were considered eligible if they met the following criteria: (1) primary localized PCa (cT1-4N0M0). (2) Patients met the definition of high-risk PCa: PSA > 20 ng/ml, or GS ≥ 8, or ≥ T3a. (3) The survival status at the end of the follow-up were clearly known.

The following criteria were used for data exclusion: (1) Multiple tumors; (2) The information of age, PSA, TNM stage, GS or follow-up time were unclear or incomplete.

2.3 Variables and main outcomes

The general characteristics, tumor information, and survival outcomes were collected.

Variables included age, race, marital status, T staging, PSA, GS, treatment, survival time, living state (alive or dead), and prostate cancer-specific living state (alive, died for prostate cancer and died for other reasons). The survival time was defined as the time from the patient's first diagnosis to the patient's death or the last follow-up time (December 31, 2015).

According to the definition of high-risk PCa, the included patients were divided into seven groups. Patients with 1 high-risk factor were in A1 (T3-4 PSA ≤ 20 ng/ml GS2-7), A2 (T1-2 PSA > 20 ng/ml GS2-7), and A3 (T1-2 PSA ≤ 20 ng/ml GS8-10). Men with two risk factors were in B1 (T3-4 PSA > 20 ng/ml GS2-7), B2 (T3-4 PSA ≤ 20 ng/ml GS8-10), and B3 (T1-2 PSA ≥ 20 ng/ml GS8-10). The group with 3 high-risk factors was C (T3-4 PSA > 20 ng/ml GS8-10).

The main outcomes in this study were overall survival (OS) and prostate cancer-specific survival (PCSS). The survival time was defined as the time from the patient's first diagnosis to the patient's death or the last follow-up time (December 31, 2015).

2.5 Statistical analyses

Baseline characteristics including age, race, marital status, T stage, GS, PSA level, and follow-up time were described in different high-risk groups. The Kaplan-Meier analysis was adopted for the OS and PCSS of men in all high-risk groups. The 5-year and 10-year OS and PCSS rate of all groups were calculated with survival tables. Long rank P values were calculated to determine the statistical significance. Univariate Cox regression model was used to evaluate each variable's parameter in predicting OS and PCSS. Multivariate Cox regression model was conducted for the variables with $P < 0.05$ in univariate analyses.

A nomogram model was built with the coefficients of each factor in the multivariate COX analysis. Verifications of the nomogram model were performed with the concordance index (C-index), and calibration curves. A C-index was used to evaluate the predictive accuracy of the nomogram. 5 and 10-year calibration curves were conducted to compare the predicted probability with the observed probability.

All statistical analyses were performed with the software of SPSS version 25 and R software version 3.2.3. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

In total, 151,799 patients with localized high-risk PCa were included, with a median age of 66 (60–72) years. 72143, 14979, and 30698 patients with only one risk factor were respectively in A1, A2, and A3 group. 5121, 16589, and 7746 patients of two risk factors severally in B1, B2, and B3 group. 4523 patients were in group C of three risk factors. The baseline characteristics were summarized in Table 1.

Table 1

Patients' characteristics of patients with all possible high-risk factors.

Characteristic	A1 (n = 72143)	A2 (n = 14979)	A3 (n = 30698)	B1 (n = 5121)	B2 (n = 16589)	B3 (n = 7746)	C (n = 4523)	Total (n = 151799)
Age (years)								
Median(IQR)	63(57 ~ 68)	69(62 ~ 76)	71(64 ~ 76)	65(58 ~ 71)	66(61 ~ 73)	73(65 ~ 80)	68(61 ~ 76)	66(60 ~ 72)
Age, n(%)								
≤ 55	12986(18)	1228(8.2)	1540(5)	816(15.9)	1572(9.5)	389(5)	492(10.9)	19023(12.5)
56–65	32186(44.6)	4167(27.8)	7502(24.4)	1978(38.6)	5910(35.6)	1669(21.5)	1403(31)	54815(36.1)
66–75	22944(31.8)	5501(36.7)	12819(41.8)	1630(31.8)	6426(38.7)	2589(33.4)	1469(32.5)	53378(35.2)
76–85	3790(5.3)	3477(23.2)	8022(26.1)	563(11)	2352(14.2)	2411(31.1)	891(19.7)	21506(14.2)
> 85	237(0.3)	606(4)	815(2.7)	134(2.6)	329(2)	688(8.9)	268(5.9)	3077(2)
Race,n(%)								
White	59318(82.2)	10310(68.8)	23888(77.8)	3737(73)	13737(82.8)	5344(69)	3339(73.8)	119673(78.8)
Black	9272(12.9)	3729(24.9)	4711(15.3)	1061(20.7)	1728(10.4)	1799(23.2)	800(17.7)	23100(15.2)
Others	3553(4.9)	940(6.3)	2099(6.8)	323(6.3)	1124(6.8)	603(7.8)	384(8.5)	9026(5.9)
Marriage								
Married	57064(79.1)	9965(66.5)	23025(75)	3438(67.1)	12875(77.6)	4994(64.5)	3019(66.7)	114380(75.3)
Unmarried	7546(10.5)	2216(14.8)	2984(9.7)	843(16.5)	1577(9.5)	1145(14.8)	647(14.3)	16958(11.2)
Separated	7533(10.4)	2798(18.7)	4689(15.3)	840(16.4)	2137(12.9)	1607(20.7)	857(18.9)	20461(13.5)
T stage								
T1	-	9080(60.6)	16693(54.4)	-	-	5330(68.8)	-	31103(20.5)
T2	46457(64.4)	5899(39.4)	14005(45.6)	2411(47.1)	6927(41.8)	2416(31.2)	1761(38.9)	79876(52.6)
T3	23885(33.1)	-	-	2336(45.6)	8812(53.1)	-	2225(49.2)	37258(24.5)
T4	1801(2.5)	-	-	374(7.3)	850(5.1)	-	537(11.9)	3562(2.3)
PSA(ng/ml)								
< 4	10099(14)	-	2615(8.5)	-	1635(9.9)	-	-	14349(9.5)
4–10	50731(70.3)	-	18716(61)	-	9243(55.7)	-	-	78690(51.8)
10–20	11313(15.7)	-	9367(30.5)	-	4631(27.9)	-	-	25311(16.7)
20–40	-	9826(65.6)	-	3306(64.6)	604(3.6)	4093(52.8)	2376(52.5)	20205(13.3)
> 40	-	5153(34.4)	-	1815(35.4)	476(2.9)	3653(47.2)	2147(47.5)	13244(8.7)
Gleason score								
≤ 7	72143(100)	14979(100)	-	5121(100)	-	-	-	92243(60.8)
8	-	-	19603(63.9)	-	7848(47.3)	4090(52.8)	1933(42.7)	33474(22.1)
9	-	-	10165(33.1)	-	8183(49.3)	3278(42.3)	2314(51.2)	23940(15.8)
10	-	-	930(3)	-	558(3.4)	378(4.9)	276(6.1)	2142(1.4)

A1: (T3-4 PSA ≤ 20 ng/ml GS2-7); A2: (T1-2 PSA > 20 ng/ml GS2-7); A3: (T1-2 PSA ≤ 20 ng/ml GS8-10); B1: (T3-4 PSA > 20 ng/ml GS2-7); B2: (T3-4 PSA ≤ 20 ng/ml GS8-10); B3: (T1-2 PSA ≥ 20 ng/ml GS8-10); C: (T3-4 PSA > 20 ng/ml GS8-10). IQR: interquartile range; PSA: prostate-specific antigen; LT: local treatment; NLT: no local treatment.

RP: radical prostatectomy; EBRT: external beam radiotherapy; COT: combined therapy; NDT: no definitive therapy.

Characteristic	A1 (n = 72143)	A2 (n = 14979)	A3 (n = 30698)	B1 (n = 5121)	B2 (n = 16589)	B3 (n = 7746)	C (n = 4523)	Total (n = 151799)
Therapy								
LT								
NLT								
RP	54124(75)	2496(16.7)	5896(19.2)	2455(47.9)	8313(50.1)	537(6.9)	1179(26.1)	75000(49.4)
EBRT	8782(12.2)	6723(44.9)	17313(56.4)	1265(24.7)	4117(24.8)	3572(46.1)	1644(36.3)	43416(28.6)
Prostatectomy	2574(3.6)	528(3.5)	1101(3.6)	371(7.2)	1764(10.6)	382(4.9)	422(9.3)	7142(4.7)
Radiation	4918(6.8)	3781(25.2)	4450(14.5)	704(13.7)	1291(7.8)	2129(27.5)	816(18)	18089(11.9)
COT	1648(2.3)	1097(7.3)	1544(5)	300(5.9)	1062(6.4)	871(11.2)	391(8.6)	6913(4.6)
NDT	97(0.1)	354(2.4)	394(1.3)	26(0.5)	42(0.3)	255(3.3)	71(1.6)	1239(0.8)
Follow up(months)								
Median(IQR)	57(33 ~ 89)	71(37 ~ 109)	68(37 ~ 104)	60(32 ~ 91)	62(34 ~ 93)	46(24 ~ 81)	51(27 ~ 81)	60(33 ~ 93)

A1: (T3-4 PSA ≤ 20 ng/ml GS2-7); A2: (T1-2 PSA > 20 ng/ml GS2-7); A3: (T1-2 PSA ≤ 20 ng/ml GS8-10); B1: (T3-4 PSA > 20 ng/ml GS2-7); B2: (T3-4 PSA ≤ 20 ng/ml GS8-10); B3: (T1-2 PSA ≥ 20 ng/ml GS8-10); C: (T3-4 PSA > 20 ng/ml GS8-10). IQR: interquartile range; PSA: prostate-specific antigen; LT: local treatment; NLT: no local treatment.

RP: radical prostatectomy; EBRT: external beam radiotherapy; COT: combined therapy; NDT: no definitive therapy.

3.2. Survival outcomes

3.2.1. OS and PCSS

The 5 and 10-year OS and PCSS rates of the overall cohort were 85.5% and 65.4%. For the seven groups, the 10-year OS rate of each group were 82.1%, 55.8%, 57.2%, 64.4%, 60.4%, 35.2% and 44.1%, individually (Table 2). Patients in A1 group had the best survival results, followed by men in B1, B2, A3, A2, B3, and C group. Men in B3 group was associated with the worst OS among all groups. Significant differences existed among seven groups. With A1 group as the reference, the HR and 95%CI of A2, A3, B1, B2, B3 and C group were 3.2(3.08 ~ 3.33), 3.03(2.93 ~ 3.14), 2.44(2.29 ~ 2.61), 2.64(2.54 ~ 2.75), 6.16(5.91 ~ 6.43), 4.87(4.61 ~ 5.15), respectively. The OS curve and HR results were shown in Fig. 1A and Table 3.

Table 2

5-year and 10-year overall survival and prostate cancer-specific survival of different groups.

Variables	OS (rate, 95%CI)		PCSS (rate, 95%CI)	
	5 year	10 year	5 year	10 year
Overall cohort	85.5% (85.3%~85.7%)	65.4% (65%~65.8%)	95.3% (95.1%~95.5%)	88% (87.6%~88.4%)
A1:T3-4, PSA ≤ 20, GS 2–7	93.7% (93.5%~93.9%)	82.1% (81.5%~82.7%)	98.9% (98.7%~99.1%)	95.8% (95.4%~96.2%)
A2:T1-2, PSA > 20, GS 2–7	79.6% (78.8%~80.4%)	55.8% (54.8%~56.8%)	94.9% (94.5%~95.3%)	86.9% (86.1%~87.7%)
A3:T1-2, PSA ≤ 20, GS 8–10	80.7% (80.3%~81.1%)	57.2% (56.4%~58%)	94.2% (93.8%~94.6%)	86.1% (85.5%~86.7%)
B1:T3-4, PSA > 20, GS 2–7	84.2% (83%~85.4%)	64.4% (62.2%~66.6%)	95.3% (94.5%~96.1%)	86.6% (85.1%~88.7%)
B2:T3-4, PSA ≤ 20, GS 8–10	82.9% (82.3%~83.5%)	60.4% (59.2%~61.6%)	92.0% (91.4%~92.6%)	80.8% (79.8%~81.8%)
B3:T1-2, PSA > 20, GS 8–10	63.6% (62.4%~64.8%)	35.2% (33.6%~36.8%)	81.7% (80.5%~82.9%)	64.7% (62.9%~66.5%)
C:T3-4, PSA > 20, GS 8–10	67.4% (65.8%~69%)	44.1% (41.7%~46.5%)	81.9% (80.5%~83.3%)	65.6% (40.1%~91.1%)
Cohort with local treatments	89.2% (89%~89.4%)	71% (70.6%~71.4%)	96.7% (96.5%~96.9%)	90.6% (90.2%~91%)
Good prognosis group	93.7% (93.5%~93.9%)	82.1% (81.5%~82.7%)	98.9% (98.7%~99.1%)	95.8% (95.4%~96.2%)
Intermediate prognosis group	81.2% (80.8%~81.6%)	58.2% (57.6%~58.8%)	93.8% (93.6%~94%)	85.1% (84.7%~85.5%)
Poor prognosis group	65.5% (64.5%~66.5%)	38.2% (36.8%~39.6%)	83.1% (82.3%~83.9%)	66.5% (64.9%~68.1%)

OS: overall survival; PCSS: prostate cancer-specific survival; 95%CI: 95% confidence interval; PSA: Prostate specific antigen; GS: Gleason score.

Table 3

Hazard ratios of patients with different high-risk factors.

HR(95%CI)	A1	A2	A3	B1	B2	B3	C
Overall cohort							
A1	1	0.31(0.3 ~ 0.32)a	0.33(0.32 ~ 0.34)a	0.41(0.38 ~ 0.44)a	0.38(0.36 ~ 0.4)a	0.16(0.16 ~ 0.17)a	0.21(0.19 ~ 0.22)a
A2	3.72(3.43 ~ 4.03)b	1	1.06(1.02 ~ 1.09)a	1.31(1.23 ~ 1.4)a	1.21(1.16 ~ 1.27)a	0.52(0.5 ~ 0.54)a	0.66(0.62 ~ 0.7)a
A3	4.05(3.78 ~ 4.33)b	1.09(1.02 ~ 1.17)b	1	1.24(1.17 ~ 1.32)a	1.15(1.11 ~ 1.19)a	0.49(0.47 ~ 0.51)a	0.62(0.59 ~ 0.66)a
B1	3.44(3.04 ~ 3.9)b	0.93(0.82 ~ 1.05)b	0.85(0.76 ~ 0.96)b	1	0.93(0.86 ~ 0.99)a	0.4(0.37 ~ 0.43)a	0.5(0.46 ~ 0.54)a
B2	5.29(4.91 ~ 5.7)b	1.42(1.32 ~ 1.53)b	1.31(1.23 ~ 1.39)b	1.54(1.36 ~ 1.74)b	1	0.43(0.41 ~ 0.45)a	0.54(0.51 ~ 0.58)a
B3	11.6(10.74 ~ 12.53)b	3.12(2.89 ~ 3.38)b	2.87(2.68 ~ 3.06)b	3.37(2.98 ~ 3.82)b	2.19(2.04 ~ 2.36)b	1	1.27(1.19 ~ 1.34)a
C	10.95(10 ~ 11.99)b	2.95(2.69 ~ 3.23)b	2.71(2.49 ~ 2.93)b	3.19(2.79 ~ 3.63)b	2.07(1.9 ~ 2.26)b	0.94(0.86 ~ 1.03)b	1
Cohort with local treatments							
A1	1	0.39(0.38 ~ 0.42)a	0.35(0.34 ~ 0.37)a	0.45(0.42 ~ 0.49)a	0.38(0.36 ~ 0.4)a	0.09(0.08 ~ 0.09)a	0.23(0.21 ~ 0.24)a
A2	2.48(2.23 ~ 2.76)b	1	0.9(0.85 ~ 0.94)a	1.15(1.05 ~ 1.26)a	0.97(0.91 ~ 1.02)a	0.32(0.3 ~ 0.35)a	0.57(0.53 ~ 0.62)a
A3	3.46(3.19 ~ 3.75)b	1.4(1.26 ~ 1.54)b	1	1.28(1.18 ~ 1.4)a	1.08(1.03 ~ 1.13)a	0.35(0.33 ~ 0.37)a	0.64(0.59 ~ 0.69)a
B1	2.99(2.55 ~ 3.51)b	1.2(1.02 ~ 1.43)b	0.86(0.74 ~ 1.01)b	1	0.84(0.77 ~ 0.92)a	0.3(0.26 ~ 0.34)a	0.5(0.45 ~ 0.55)a
B2	5.05(4.62 ~ 5.51)b	2.03(1.83 ~ 2.26)b	1.46(1.35 ~ 1.58)b	1.69(1.44 ~ 1.98)b	1	0.46(0.42 ~ 0.49)a	0.59(0.55 ~ 0.64)a
B3	9.16(8.27 ~ 10.15)b	3.69(3.28 ~ 4.16)b	2.65(2.41 ~ 2.91)b	3.07(2.59 ~ 3.63)b	1.82(1.64 ~ 2.01)b	1	1.13(1.04 ~ 1.23)a
C	9.82(8.74 ~ 11.04)b	3.96(3.48 ~ 4.51)b	2.84(2.55 ~ 3.17)b	3.29(2.76 ~ 3.92)b	1.95(1.74 ~ 2.18)b	1.07(0.95 ~ 1.22)b	1

HR: Hazard ratios; CI: confidence interval; GS: Gleeson score. A1: T3-4 PS ≤ 20 ng/ml GS2-7; A2: T1-2 PS > 20 ng/ml GS2-7; A3: T1-2 PS ≤ 20 ng/ml GS8-10; B1: T3-4 PS > 20 ng/ml GS2-7; B2: T3-4 PS ≤ 20 ng/ml GS8-10; B3: T1-2 PS ≥ 20 ng/ml GS8-10; C: T3-4 PS > 20 ng/ml. a: overall survival; b: prostate cancer-specific survival.

The 5- and 10- year PCSS rate of the overall cohort were 95.3% and 88%. The 10-year PCSS rate of each of these groups were 95.8%, 86.9%, 86.1%, 86.9%, 80.8%, 64.7% and 65.6%, respectively (Table 2). Men in A1 group still had the best PCSS, followed by A2, B1, A3, B2, C and B3 group. No significant difference was detected between A2 and B1 group [HR: 1.08, 95%CI (0.95 ~ 1.22)], as well as between B3 and C group [HR: 0.94, 95%CI (0.86 ~ 1.03)]. With men in A1 group as the reference, the HR and 95%CI of A2, A3, B1, B2, B3 and C group were 3.72(3.43 ~ 4.03), 4.05(3.78 ~ 4.33), 3.44(3.04 ~ 3.9), 5.29(4.91 ~ 5.7), 11.6(10.74 ~ 12.53), 10.95(10 ~ 11.99), respectively. These results were presented in Fig. 1B and Table 3.

For the cohort that have received local treatments, the 10-year OS and PCSS rate were 71% and 90.6% (Table 2).The OS curve was shown in Fig. 1C, and PCSS curve in Fig. 1D. The survival outcomes were similar with those of overall cohort. Men with the best prognosis were in A1 group and the worst were in B3 and C group. The results of the rest groups including A2, A3, B1 and B2 were close. With A1 group as the reference, the HR and 95%CI of A2, A3, B1, B2, B3 and C group for PCSS were 2.48(2.23 ~ 2.76), 3.46(3.19 ~ 3.75), 2.99(2.55 ~ 3.51), 5.05(4.62 ~ 5.51), 9.16(8.27 ~ 10.15), 9.82(8.74 ~ 11.04), respectively (Table 3).

According to the OS and PCSS results in all and local treatment cohort, three simplified groups were divided: a good prognosis group with only one high-risk factor of T3 – 4 (A1), an intermediate prognosis group with one factor of PSA ≥ 20 ng/ml, or GS 8–10 (A2, A3, B1 and B2), and a poor prognosis group of PSA ≥ 20 ng/ml and GS 8–10 with/without T3-4 (B3 and C). The OS and PCSS curves of the three groups were

shown in Fig. 2. The 5- and 10-year OS rate of these three groups were 93.7% vs 81.2% vs 65.5%, and 82.1% vs 58.2% vs 38.2%, respectively (Table 2). With the good prognosis group as the reference, the HR and 95%CI of the intermediate and the poor prognosis group for overall morality were2.94 (2.86 ~ 3.03) and 5.68 (5.47 ~ 5.90). As for the results of PCSS, the 5- and 10- year rate of three groups were 98.9% vs 93.8% vs 83.1%, and 95.8% vs 85.1% vs 66.5% (Table 2). Compared to the good prognosis group, the HR of the intermediate and the poor prognosis group were 4.21(3.96 ~ 4.48) and 11.36 (10.59 ~ 12.19).

3.3. Multivariate COX analysis

The results of multivariate Cox regression results for overall mortality and cancer-specific mortality were summarized in Table 4. Univariate COX analyses showed that the p values of factors including age, race, marital status, high-risk factors and therapy were < 0.05. Multivariate COX regression analysis was conducted with these factors. With A1 as the reference, the HR and 95% CI of A2, A2, A3, B1, B2, B3 and C group for overall mortality were 1.71 (1.64 ~ 1.78), 1.8 (1.74 ~ 1.87), 1.82 (1.7 ~ 1.94), 2.06 (1.98 ~ 2.15), 2.67 (2.56 ~ 2.8), 2.96 (2.8 ~ 3.14). As for the cancer-specific morality, the HR and 95% CI of A2, A2, A3, B1, B2, B3 and C group were 2.38 (2.19 ~ 2.59), 2.96 (2.75 ~ 3.18), 2.75 (2.42 ~ 3.11), 4.48 (4.16 ~ 4.84), 6.45 (5.94 ~ 7.01), 7.7 (7.02 ~ 8.45), respectively.

Table 4
Multivariate COX analysis for patients with high-risk prostate cancer.

Risk factors	Overall morality			Cancer-specific morality		
	HR	95%CI	P	HR	95%CI	P
Age						
≤ 55	1		Ref.	1		Ref.
55–65	1.46	(1.38 ~ 1.56)	< 0.001	1.12	(1.03 ~ 1.23)	0.014
65–75	2.5	(2.35 ~ 2.65)	< 0.001	1.45	(1.32 ~ 1.58)	< 0.001
76–85	4.6	(4.32 ~ 4.9)	< 0.001	2.15	(1.95 ~ 2.36)	< 0.001
> 85	8.84	(8.24 ~ 9.48)	< 0.001	3.76	(3.36 ~ 4.22)	< 0.001
Race						
White	1		Ref.	1		Ref.
Black	1.16	(1.12 ~ 1.19)	< 0.001	1.13	(1.07 ~ 1.19)	< 0.001
Others	0.75	(0.71 ~ 0.79)	< 0.001	0.83	(0.76 ~ 0.9)	< 0.001
Marital status						
Married	1		Ref.	1		Ref.
Unmarried	1.3	(1.26 ~ 1.35)	< 0.001	1.34	(1.26 ~ 1.43)	< 0.001
Divorced	1.38	(1.34 ~ 1.42)	< 0.001	1.38	(1.31 ~ 1.46)	< 0.001
Risk						
A1	1		Ref.	1		Ref.
A2	1.71	(1.64 ~ 1.78)	< 0.001	2.38	(2.19 ~ 2.59)	< 0.001
A3	1.8	(1.74 ~ 1.87)	< 0.001	2.96	(2.75 ~ 3.18)	< 0.001
B1	1.82	(1.7 ~ 1.94)	< 0.001	2.75	(2.42 ~ 3.11)	< 0.001
B2	2.06	(1.98 ~ 2.15)	< 0.001	4.48	(4.16 ~ 4.84)	< 0.001
B3	2.67	(2.56 ~ 2.8)	< 0.001	6.45	(5.94 ~ 7.01)	< 0.001
C	2.96	(2.8 ~ 3.14)	< 0.001	7.7	(7.02 ~ 8.45)	< 0.001
Therapy						
RP	1		Ref.	1		Ref.
EBRT	1.33	(1.29 ~ 1.38)	< 0.001	1.15	(1.08 ~ 1.22)	< 0.001
Prostatectomy	1.44	(1.36 ~ 1.52)	< 0.001	1.74	(1.6 ~ 1.9)	< 0.001
Radiation	2.18	(2.1 ~ 2.26)	< 0.001	2.27	(2.13 ~ 2.43)	< 0.001
COT	1.89	(1.75 ~ 2.05)	< 0.001	2.68	(2.38 ~ 3.02)	< 0.001
NDT	2.28	(2.05 ~ 2.54)	< 0.001	2.52	(2.09 ~ 3.03)	< 0.001

HR: hazard ratio; 95%CI: 95% confidence interval; Ref: reference; PSA: prostate-specific antigen; GS: Gleason score; RP: radical prostatectomy; EBRT: external beam radiotherapy; COT: combined therapy; NDT: no definitive therapy.

3.4. Nomogram predicting model and validation

The predicting model of nomograms was built with the factors in the multivariate COX analysis (Fig. 3). The C-index of this nomogram was 0.773, indicating a good discrimination ability of this model. 5- and 10-year calibration curves (Fig. 4) also revealed good agreement between the actual observation and the nomogram prediction.

4. Discussion

The prognosis of men with high-risk PCa has been investigated in many previous publications. The 10-year PCSS rate of men with localized high-risk PCa is approximately 90% [14–16]. Detailed high-risk factors and the number of high-risk factors have a great impact on the survival outcome of patients, and only a few studies have reports on this [13, 17–19].

A total of 151,799 patients with high-risk PCa were enrolled in our study. The overall 10-year OS and PCSS rates were 65.4% and 88% in all patients, and 71% and 90.6% in the patients that have undergone local treatments. According to the OS and PCSS results, we divided them into three groups: a good prognosis group with only one high-risk factor of T3 − 4 (A1), an intermediate prognosis group with one factor of PSA > 20 ng/ml, or GS 8–10 (A2, A3, B1 and B2), and a poor prognosis group of PSA > 20 ng/ml and GS 8–10 with/without T3-4(B3 and C). The 10-year OS and PCSS rate of the three groups were 82.1% vs 58.2% vs 38.2% and 95.8% vs 85.1% vs 66.5%, respectively. Joniau et al. [17] retrospectively analyzed 1360 high-risk PCa patients treated with radical prostatectomy with pelvic lymphadenectomy. They developed an extended model of all seven groups and a simplified model of three subgroups: a good prognosis subgroup (one single high-risk factor); an intermediate prognosis subgroup (PSA > 20 ng/ml and stage cT3-4); and a poor prognosis subgroup (GS 8–10 in combination with at least one other high-risk factor). In their study, the 10-year PCSS rates of the good, intermediate, and poor prognosis subgroups were 95.4%, 88.3%, 79.7%, and the 10-year OS rates were 84.0%, 68.7%, and 59.1%, respectively. Vagnoni et al. [20] evaluated 615 high-risk PCa patients and found that the 10-year cancer-specific mortality-free survival rates of men with 1, 2, 3 high-risk factors were 92.8%, 84.2%, and 27.7%, respectively. Some other studies [18, 21] found that significant differences of biochemical failure-free survival existed among the patients with 1, 2, 3 high-risk factors of PCa. Walz et al. [13] analyzed 887 high-risk PCa patients treated with radical prostatectomy. They found that the 5-year BCR survival of only one D'Amico risk factor was 50.3%, compared with 27.5% for patients with two or more risk factors. Tai et al. [22] revealed that men with only one risk factor had a 5-year BCR-free survival rate of 76.9%, compared with 34.6% in men with ≥ 2 risk factors. Gomez-Iturriaga et al.[23] identified 1341 extreme-risk PCa (T3b-4, GS 9–10 or PSA > 50 ng/ml; or patients with 2 or more high-risk factors: T2c-3a, GS 8 and PSA > 20 ng/ml), and the 10-year BCR, clinical-free survival, PCSS and OS were 57.0%, 78.9%, 93.6%, and 71.3%, respectively.

The PCSS curve of seven groups showed that men with one risk factor of T3-4 had the best survival, and men with one risk factor of PSA > 20 ng/ml had similar survival outcomes with those with two high-risk factors of T3-4 and PSA > 20 ng/ml. Besides, men with two factors of PSA > 20 ng/ml and GS 8–10 were associated with similar PCSS with men with all three high-risk factors. These results revealed that clinical T staging has less impact on the prognosis when compared with other high-risk factors of PSA and GS. The survival outcomes of men with PSA > 20 ng/ml had obviously better survival outcomes than men with GS 8–10, but were significantly worse than those with T3-4. Men with two high-risk factors of GS 8–10 and T3-4 had significantly worse prognoses than those with PSA > 20 ng/ml and T3-4. These results revealed that the factor of GS 8–10 is more aggressive than PSA > 20 ng/ml. Some studies [17, 18] reported that GS 8–10 was the most important predictor of prostate cancer, followed by PSA > 20 ng/ml and then stage cT3.Walz et al. [13] reported that men with cT3 had the lowest biochemical recurrence-free survival, followed by men with PSA ≥ 20 ng/ml and GS 8–10.

Univariate and multivariate COX analysis showed that age, race, marital status, T stage, PSA level, GS, therapy were the independent risk factors of high-risk PCa. A study [24] indicated that risk factors of PCa included family history, genetics, age, ethnicity, and tumor characteristics. The nomogram was constructed with risk factors in multivariate COX analyses. This model is an intuitionistic and convenient tool for predicting survival rates. With this predicting model, the 5- and 10-year survival rates of each patient with high-risk PCa can be estimated. The C-index of our nomogram model was 0.773, indicating that the model has good accuracy. The 5- and 10-year calibration curves revealed a good agreement between the actual observation and the nomogram prediction.

However, there were some limitations in our study. Firstly, our study was a retrospective analysis in which there were some unavoidable confounders and risk biases. It may interfere with the results. Secondly, our nomogram model was built on high-risk populations and was only applicable to survival prediction of men with high-risk PCa. Thirdly, due to the limitations of the SEER database, many important endpoints such as BCR-free survival, progression-free survival could not be analyzed. Lastly, even though the survival results and the nomogram were conducted with a large cohort and the validation of the nomogram model seemed to be reliable, high-quality studies are still needed for further validations.

5. Conclusions

The GS 8–10 and PSA > 20 ng/ml was associated with the poorest prognoses in high-risk PCa patients. Prostate cancer with three high-risk factors was not more aggressive than that with two high-risk factors of GS 8–10 and PSA > 20 ng/ml. With the independent risk factors of age, race, marital status, T stage, PSA level, GS, therapy, a predicting model of nomogram was built and validated.

Abbreviations

SEER: Surveillance, Epidemiology and End Results; PSA: prostate-specific antigen; GS: Gleason score; RP: radical prostatectomy; EBRT: external beam radiotherapy; OS: overall survival; PCSS: prostate cancer-specific survival; HR: hazard ratio; 95%CI: 95% confidence interval;

BCR: biochemical recurrence; C-index: Concordance index; A1: T3-4 PSA≤20ng/ml GS2-7; A2: T1-2 PSA>20ng/ml GS2-7; A3: T1-2 PSA≤20ng/ml GS8-10; B1: T3-4 PSA>20ng/ml GS2-7; B2: T3-4 PSA≤20ng/ml GS8-10; B3: T1-2 PSA≥20ng/ml GS8-10; C: T3-4 PSA>20ng/ml GS8-10.

Declarations

Acknowledgments

We would like to thanks the SEER program for providing the open-source data.

Availability of data and materials

Data for this study were obtained from the US NCI SEER database (https://seer.cancer.gov)

Ethical Approval

All data were from the public database, no ethical approval was required.

Consent for publication

Not applicable

Conflict of Interest

The authors have no competing interests.

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Figures

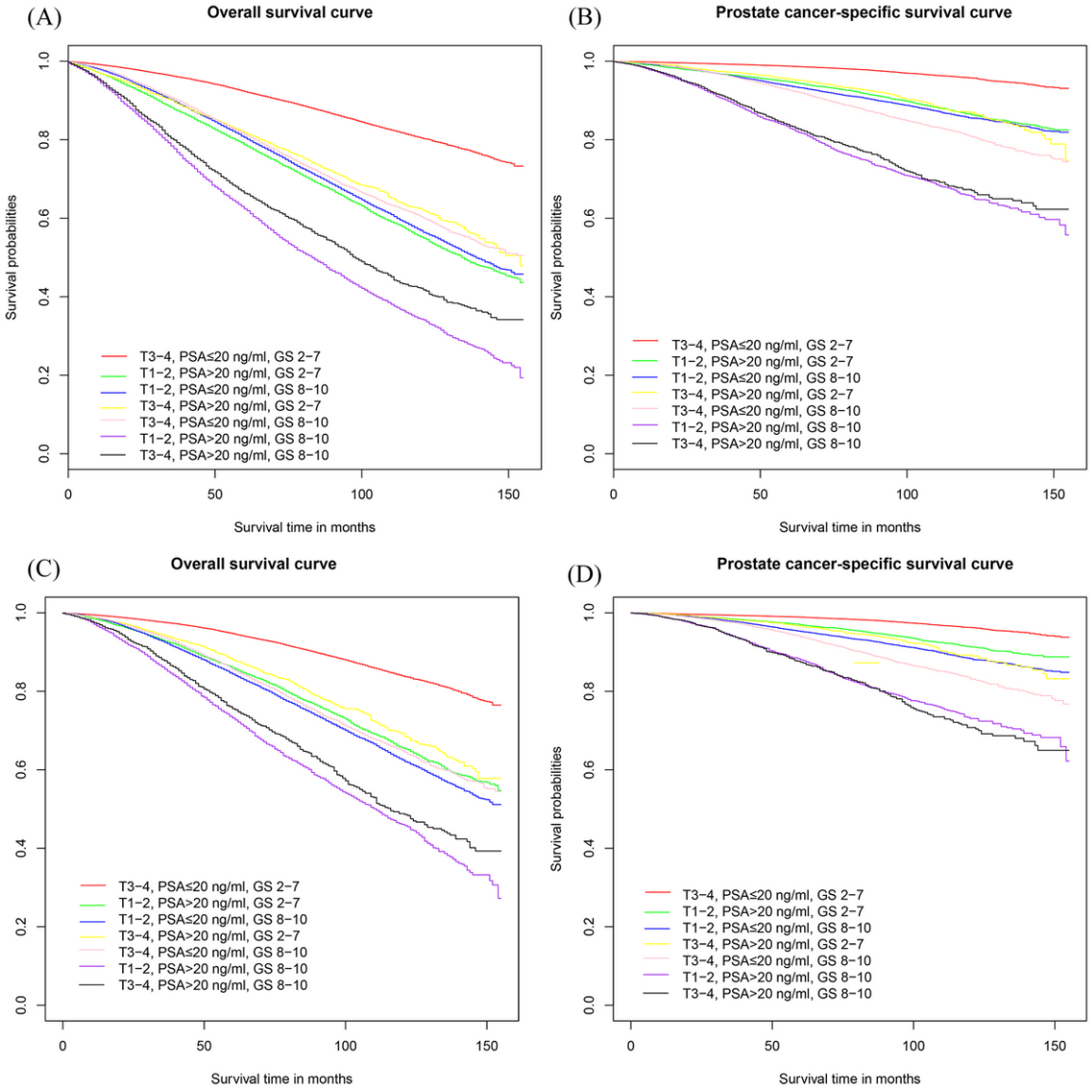

Figure 1

The survival curves of all possible high-risk groups. (A) The overall survival curve of overall cohort. (B) The prostate cancer-specific survival curve of overall cohort. (C) The overall survival curve of cohort with local treatments. (D) The prostate cancer-specific survival curve of cohort with local treatments.

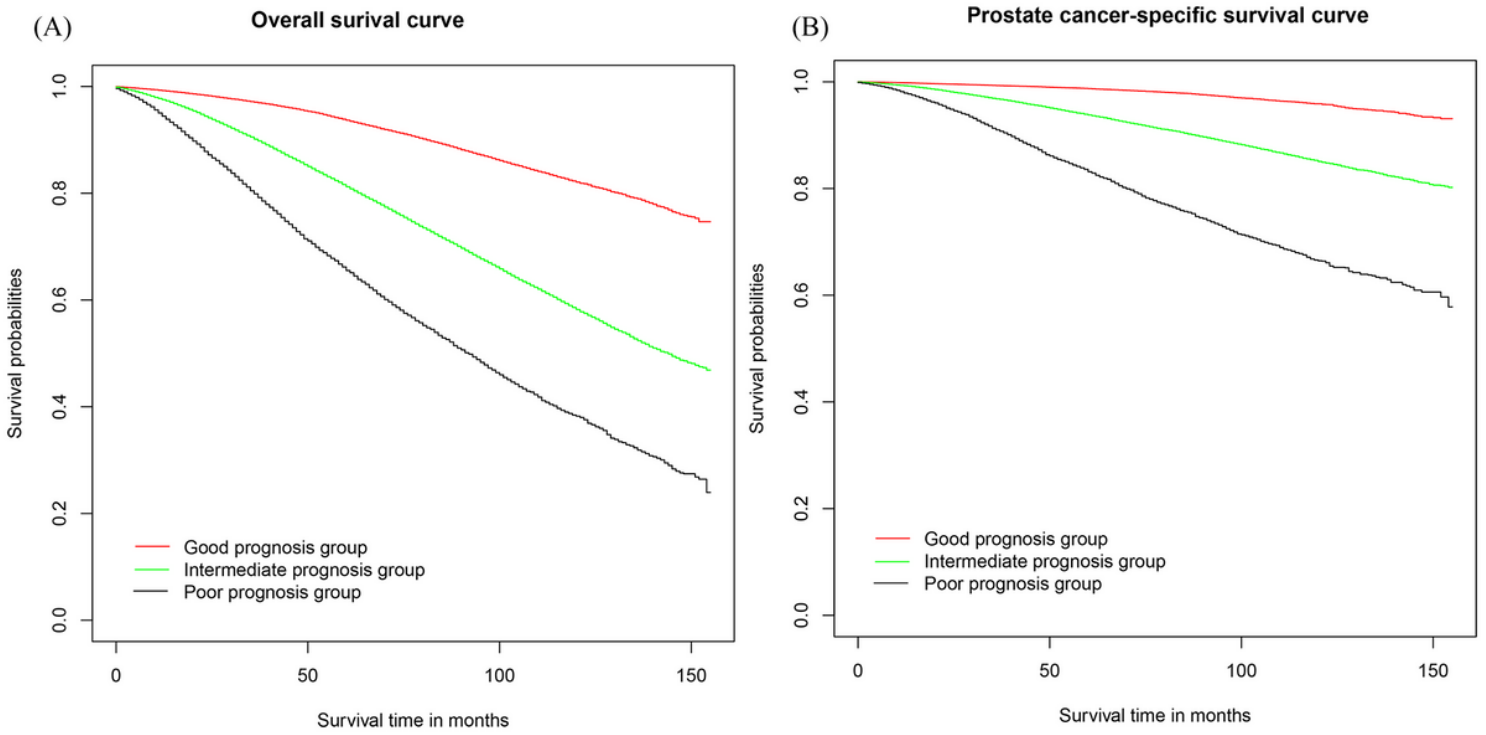

Figure 2

The survival curves of good, intermediate and poor prognosis groups. (A) The overall survival curve of three prognosis groups. (B) The prostate cancer-specific survival curve of three prognosis groups.

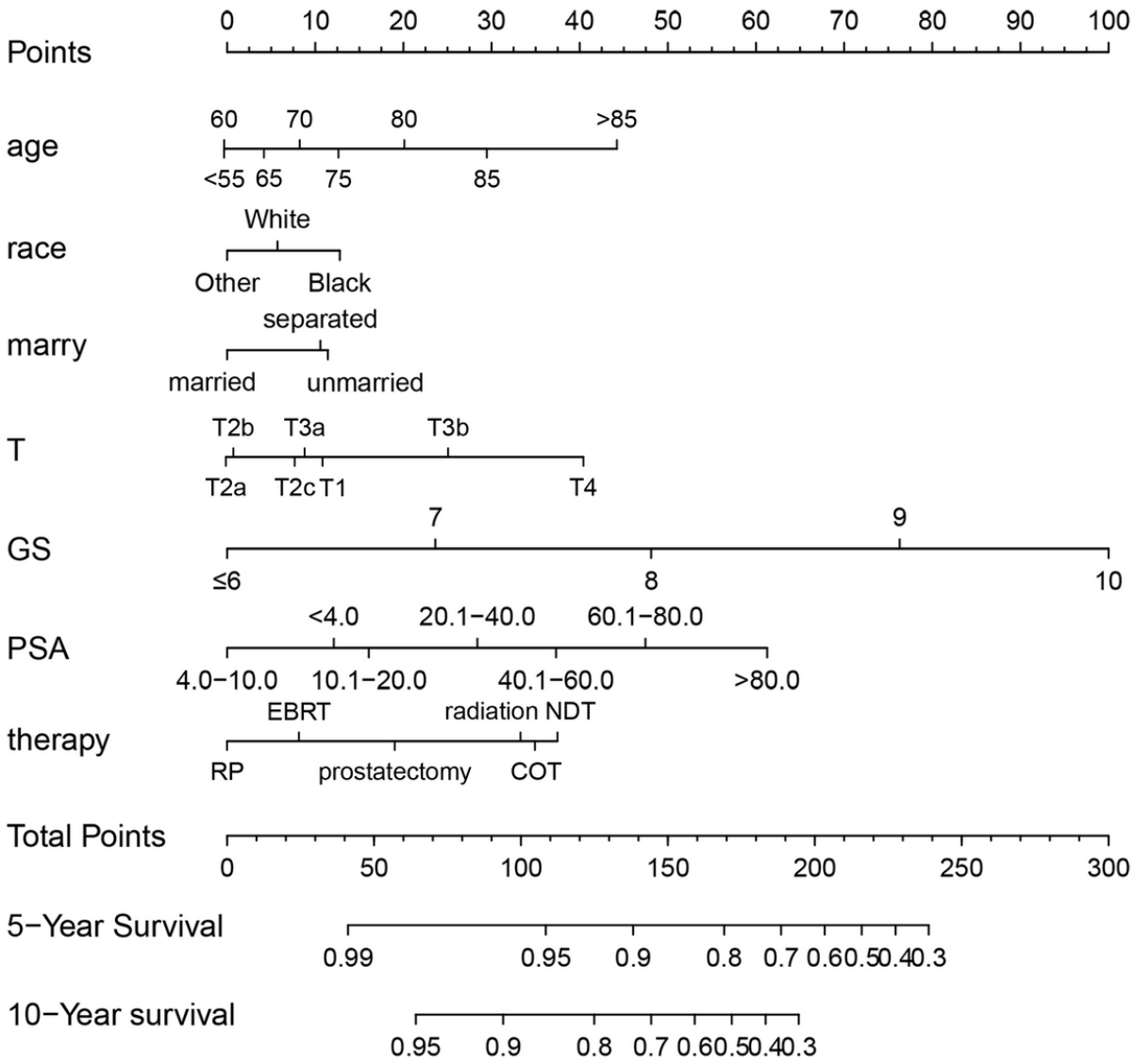

Figure 3

The nomogram model of predicting the probability of PCSS in men with high-risk PCa based on the factors of age, race, marital status, T stage, PSA, GS and therapy. Instructions: Locate the patient's level of every factor on the axis. Draw a line straight upward to the point axis to determine the points received from each factor. Sum all points of each factor and locate the final sum on the total-point axis. Draw a line straight down to find the patient's 5- and 10-year PCSS rates.

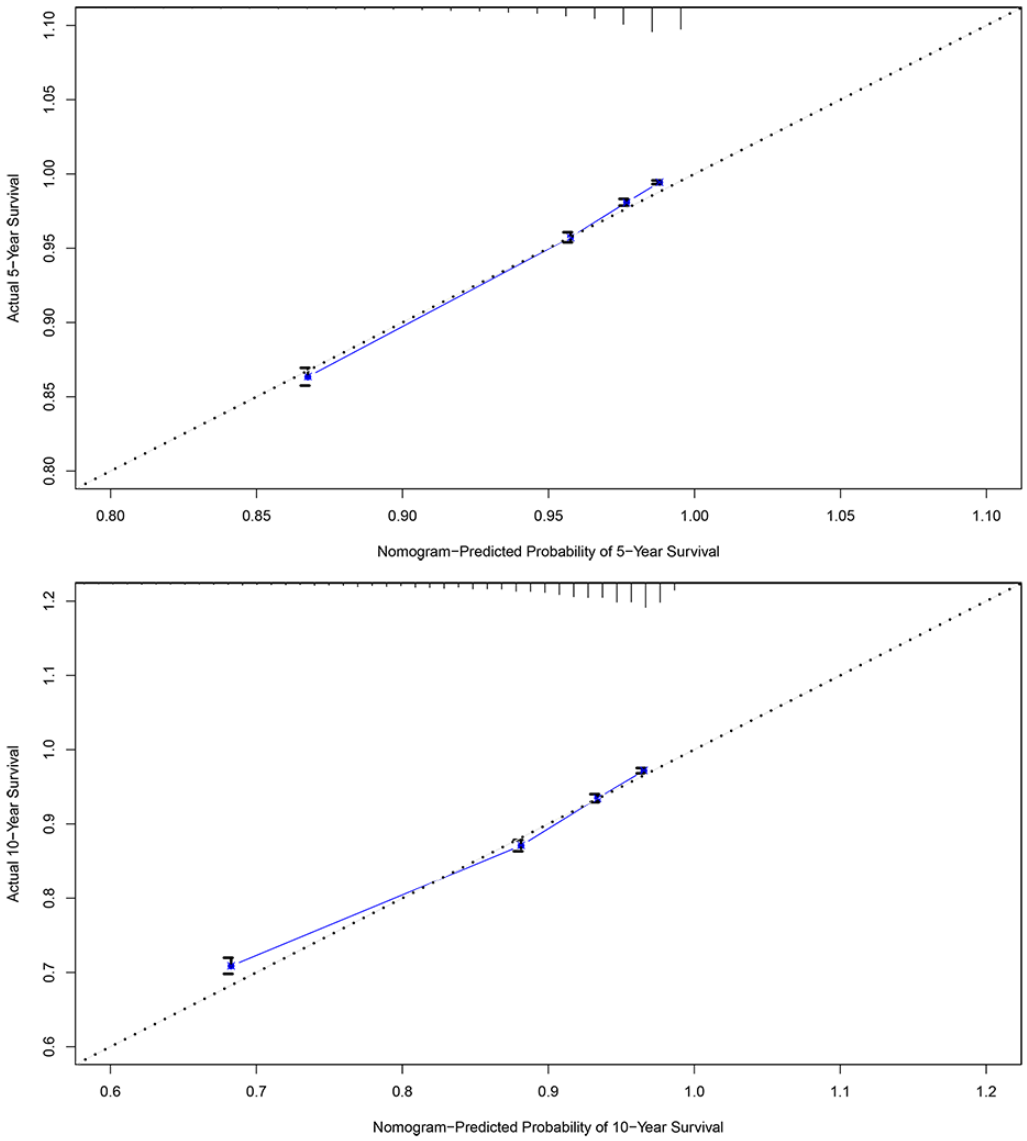

Figure 4

Nomogram calibration curves of the probability of 60-, and 120 months PCSS between the prefect prediction and the actual nomogram. The 45-degree gray dotted line indicates a perfect prediction. The blue polyline represented the actual nomogram. (A) Nomogram calibration curves of the probability of 60 months PCSS. (B) Nomogram calibration curves of the probability of 120 months PCSS.