Prognostic Nomogram for Penile Cancer, an Analysis Based on SEER Database

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Abstract

Background: We aimed to establish a prognostic nomogram for Penile Cancer (PC) patients based on the Surveillance, Epidemiology, and End Results Program (SEER) database.

Methods: Data of 1694 patients between 2010 and 2015 were downloaded and extracted from the SEER database. Then, they were randomly divided into the development group (70%) and the verification group (30%). Following, the univariate and multivariate Cox proportional hazards regression was respectively used to explore the possible risk factors of PC. Factors which significantly related to the overall survival (OS) were used to establish the nomogram. Further, the concordance index (C-index), receiver operating characteristic curve (ROC) and calibration curve were used to assess the nomogram, respectively. An internal validation was carried out to test the accuracy and effectiveness of nomogram. Finally, the Kaplan-Meier calculation was used to predict the further survival status of these patients.

Results: Multivariate Cox proportional hazards regression demonstrated that the independent prognostic risk factors associated with PC were age, stage T, N and M, and grade, with a moderate c-index of 0.732 [95% confidence interval (CI), 0.706-0.757] in development group and 0.743 (95% CI, 0.703-0.782) in verification group. Meanwhile, the areas under the ROC (AUC) of 3-year and 5-year survival were 0.739 and 0.727, respectively. The survival calibration curves of 3-year and 5-year brought out a high consistency.

Conclusion: Our study obtained a satisfactory nomogram to reveal the survival of PC patients, which could be helpful for clinicians to assess the situation of PC patients and to implement the further treatment.

Introduction

Although the incidence increased slightly in some areas in recent years, penile cancer (PC) was still a relatively rare malignancy in developed countries [1–3]. It had been showed that multiple etiologies might have contributed the occurrence of this disease, such as human papillomavirus (HPV) infection, phimosis, lichen sclerosus, smoking, condylomata acuminate, sexual problems, and chronic inflammation, etc. [4–10].

Because of its high mortality, a clinical model to predicting the prognosis of PC patients would be necessary [11]. Although the TNM stage and pathological classification systems, from the 8th American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), were widely used to predict the survival of PC patients [12, 13], a lot of limitations existed. However, the SEER database had collected the detailed information of PC patients, which allowed us to build a reliable prognostic nomogram.

Materials And Methods

After registered an account and signed a Data Agreement on SEER database website, we were authorized to download all data of PC patients using the SEER ∗ Stat version 8.3.5 software. All available data on the patients' age, race, stage T/N/M (AJCC 7th standard 2010+), grade, survival time, and live status were collected. Cases with unknown, undefined and missing data were excluded. "Caret" package of R version 3.6.0 software was utilized to randomize the patients into development group (70%) and verification group (30%). In addition, in our study, patients whose race was not black or white were described as "others".

R version 3.6.0 software with “foreign”, “survival”, “survminer” and “rms” packages was used to all statistical analyses, and P value < 0.05 was regarded to be statistically significant. Every parameter was firstly calculated by the univariate and multivariate Cox proportional hazards regression model and resulted as hazard ratio (HR) and 95% confidence interval (CI). Then, possible risk factors were identified. Finally, the prognostic nomogram using data from the development group was conducted to predict patients’ further survival.

C-index, AUC and calibration curves of 3-year and 5-year survival were calculated to verify the accuracy of the nomogram. Higher C-index and more AUC meant higher quality. As many as possible of bootstraps with 3000 resamples were set up to make sure the precision of 3- and 5-year calibrations in the comparison between the predicted and observed survival. Further, the Kaplan-Meier analysis was also used to demonstrate patients’ possible survival.

Results

According to the screening criteria, 7315 males between 2010 and 2015 were involved in our study, from which 5621 patients were excluded because of incomplete clinical information and lack of TNM stage based on 7th AJCC standard (2010+). Eventually, 1694 patients were included, which were randomly divided into the development group (1188 patients) and the validation group (506 patients). The characteristics of these patients were summarized in Table 1.

Table 1

Characteristics of 1694 patients suffered penile cancer in SEER[1] database						
Factors	**Total**	**%**	**Development group**	**%**	**Validation group**	**%**
Age						
< 50	197	11.6	137	11.5	60	11.9
50–59	292	17.3	222	18.7	70	13.8
60–69	419	24.7	284	23.9	135	26.7
70–79	415	24.5	299	25.2	116	22.9
> 80	371	21.9	246	20.7	125	24.7
Race						
black	163	9.6	123	10.4	40	7.9
white	1442	85.1	1005	84.6	437	86.4
others[2]	89	5.3	60	5.0	29	5.7
Stage_T						
stage_T1a	475	28.1	334	28.1	141	27.9
stage_T1b	186	11.0	143	12.0	43	8.5
stage_T1NOS	221	13.0	147	12.4	74	14.6
stage_T2	427	25.2	290	24.4	137	27.0
stage_T3	295	17.4	211	17.7	84	16.6
stage_T4	41	2.4	28	2.4	13	2.6
stage_Ta	10	0.6	7	0.6	3	0.6
stage_Tx	39	2.3	28	2.4	11	2.2
Stage_N						
stage_N0	1291	76.2	911	76.8	380	75.1
stage_N1	105	6.2	70	6.0	35	6.9
stage_N2	113	6.7	76	6.4	37	7.3
stage_N3	119	7.0	82	6.9	37	7.3
stage_Nx	66	3.9	46	3.9	20	3.4
Stage_M						
stage_M0	1631	96.2	1146	96.5	485	95.8
stage_M1	63	3.8	42	3.5	21	4.2
Grade						

Characteristics of 1694 patients suffered penile cancer in SEER[1] database						
grade_I	468	27.6	309	26.0	159	31.4
grade_II	822	48.6	592	49.8	230	45.5
grade_III	390	23.0	273	23.0	117	23.1
grade_IV	14	0.8	14	1.2	0	0

[1]: the Surveillance, Epidemiology, and End Results Program; [2]: included patients whose race were not black or white.

In development group, the median follow-up was 32 (95% CI, 30–36) months. However, the median of survival time was not applicable. (Fig. 1)

Univariate Cox proportional hazards regression demonstrated that age, stage T, N and M, and grade were significantly related to the survival of PC patients. Furthermore, results of multivariate cox regression showed that there were multiple prognostic factors were strongly independent, including age, stage T2, stage T3, stage T4, stage Tx, stage N, stage M1, and grade III. However, weak but insignificant correlation was found for stage T1b. Additionally, race was not independent both in univariate and multivariate Cox analyses. (Table 2)

Table 2

univariate and multivariate Cox analyses based on penile cancer patients in development group								
	univariate analyses				multivariate analyses			
Factors	HR[1]	lower.95	upper.95	P value	HR[1]	lower.95	upper.95	P value
Age(< 50 reference)								
50–59	1.289	0.8023	2.071	0.29406	1.2734	0.7893	2.054	0.321967
60–69	1.368	0.8711	2.148	0.17373	1.3936	0.8847	2.195	0.152280
70–79	1.813	1.1692	2.812	0.00785 **	1.9309	1.2370	3.014	0.003781 **
> 80	4.022	2.6237	6.165	1.7e-10 ***	4.3389	2.8015	6.720	4.86e-11 ***
Race(black reference)								
white	0.8191	0.6015	1.116	0.206	0.8501	0.6175	1.170	0.319690
Others[2]	0.9009	0.5376	1.510	0.692	0.9275	0.5453	1.578	0.781204
Stage(stage_T1a reference)								
stage_T1b	1.908	1.3157	2.768	0.00066 ***	1.4984	0.9613	2.335	0.074140 .
stage_T1NOS	1.311	0.8853	1.942	0.17645	1.3575	0.9109	2.023	0.133176
stage_T2	2.124	1.5653	2.883	1.32e-06 ***	1.5679	1.1286	2.178	0.007339 **
stage_T3	2.664	1.9410	3.655	1.30e-09 ***	1.8276	1.2832	2.603	0.000833 ***
stage_T4	5.402	3.2049	9.104	2.41e-10 ***	4.7712	2.7571	8.257	2.35e-08 ***
stage_Ta	1.240	0.3037	5.064	0.76435	2.0969	0.5036	8.731	0.308958
stage_Tx	4.461	2.5452	7.820	1.76e-07 ***	2.3185	1.2088	4.447	0.011385 *
Stage(stage_N0 reference)								
stage_N1	2.017	1.410	2.885	0.000123 ***	1.6712	1.1364	2.458	0.009055 **
stage_N2	2.159	1.522	3.062	1.58e-05 ***	1.6684	1.1417	2.438	0.008184 **
stage_N3	2.868	2.079	3.957	1.38e-10 ***	2.1150	1.4838	3.015	3.45e-05 ***

univariate and multivariate Cox analyses based on penile cancer patients in development group								
stage_Nx	2.242	1.422	3.536	0.000512 ***	1.8153	1.0721	3.074	0.026486 *
Stage(stage_M0 reference)								
stage_M1	4.53	3.049	6.732	7.67e-14 ***	2.8295	1.8255	4.386	3.29e-06***
Grade(grade_I reference)								
grade_II	1.818	1.381	2.391	1.97e-05 ***	1.2674	0.9407	1.708	0.119162
grade_III	2.660	1.976	3.580	1.09e-10 ***	1.5069	1.0343	2.196	0.032714 *
grade_IV	2.706	1.091	6.711	0.0317 *	1.3686	0.5266	3.557	0.519587
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1								
[1]: hazard ratio; [2]: included patients who were not black or white.								

Prognostic nomogram involved all risk factors based on the data of development group was showed in Fig. 2. Corresponding scores were assigned to each factor, and the sum of scores reflected the 3-year and 5-year survival and mortality of patients. C-index of the nomogram model on the basis of development group was 0.732 (95% CI, 0.706–0.757). The result was reported to be 0.743 (95% CI, 0.703–0.782) in the verification group, which was significantly superior to that in development group.

The AUC of 3- and 5-year survival were 0.739 and 0.727 (Fig. 3), which indicated the reliability of the nomogram. The 3- and 5-year calibration curves of development group also showed satisfying consistency between the observed and predicted outcomes (Fig. 4).

More intuitional differences were showed in Kaplan-Meier analyses (Fig. 5, A-G). Function of “coxph” package was used to build the proportional-risk model. After comparing with the median risk, patients were divided into high-risk and low-risk groups, from which the high-risk group gained lower survival in 3 years (44.5%, 95% CI, 39.9% − 49.6%) and 5 years (35.9%, 95% CI, 30.6% − 42.3%) ($P < 0.0001$) (Fig. 5, A). Further, patients with age of > 80 and 70–79 showed significantly lower survival compared with the younger ($P < 0.0001$) (Fig. 5, B). Significant differences of Kaplan-Meier curves were observed in stage T, N and M, and grade as well (Fig. 5, C-F). However, no significant difference could be found among patients with different races, though the white patients had a slight but insignificant advantage in long-term survival ($P = 0.43$) (Fig. 5, G).

C-index, AUC and calibration curves were respectively used to evaluate the accuracy of the nomogram. On the basis of the verification group, statistical results showed that the C-index was 0.743 (95% CI, 0.703–0.782), which was higher than 0.7 and better than the development group. Meanwhile, the AUC of 3- and 5-year survival in validation group were 0.725 and 0.729, respectively (Fig. 6). The observed-predicted calibration curves of 3- and 5-year also showed similar results (Fig. 7). All of these results proved the worth of the nomogram.

Discussion

Although there were some differences in hygienic, social and religious practice [14], PC, mostly squamous cell carcinoma [15], was still a rare disease over the past decades [16–18]. In most developed areas, the incidence of PC was even decreasing gradually [19, 20]. However, due to uncommon clinical cases and lack of reliably prognostic tools in assessment, clinicians seemed to have limited method in understanding and predicting the prognosis of PC.

As a tool for predicting patients' prognosis, nomogram was widely used in oncology, such as bladder cancer, prostatic cancer and breast cancer [21–23]. Its capability was to provide a more individualized prognostic assessment for patients by combining various prognostic risk factors which had been widely recognized [24]. Our prognostic nomogram was based on the database of SEER, which had collected the detailed information of approximately 34.6 percent of the U.S. population [25].

In our study, elderly patients, especially those older than 80, would have a significantly lower 3-year (34.6%, 95% CI, 27.9%-42.7%) and 5-year (23.5%, 95% CI, 16.4%-33.7%) survival ($P < 0.0001$). Simultaneously, these patients were also weighted more points than others. Kaplan-Meier curve of age showed that only slight difference in OS could be found among all groups under 70 (643/1188 of development group). These evidences proved that elder age might be an independent risk factor for the prognosis of PC patients, which was consistent with most studies [18].

According to the study by Sharma et al., black males who were suffered from PC would have a worse OS [26]. In addition, Slopnick et al. declared that African-American PC patients probably had a higher risk of death compared with the white [27]. However, in our study, both in the result of cox regression and Kaplan-Meier curve, no significant difference was found in the comparison among white, black and other races. This might be helpful to explore the real answer of higher mortality rate in some areas, instead of the superiority of race.

Furthermore, results of cox regression analyses also suggested the importance of cancer stage in the prognostic evaluation of patients. But it seemed to be not significant among some subgroups, including stage T1a, stage T1b and stage T1NOS. Similar to most studies, lymph node involvement and distant metastasis remained independent risk factors for patients' prognosis [28].

The recent guideline on PC from European Association of Urology strongly affirmed the importance of strict grade in pathological assessment [29]. Aita et al. claimed that high histopathological grade was responsible for a poor prognosis based on a study with an average follow-up more than 3 years involving 163 PC patients [30]. Other studies also emphasized the importance of pathologic grade [31, 32]. But, in our study, it seemed that the histopathological grade played a different role in the assessment of patients' prognosis except for the grade III. However, for Grade IV, only 14 (0.8%) patients were included, which might cause a statistical bias.

Above all, some limitations in our study must be taken into consideration. Firstly, the SEER database was a retrospective resource library including patients over a long period span, which might lead to an inevitable bias. Secondly, data about habit, custom (especially for sexual activity), human papilloma virus infection, average income, religion, smoking, education, Charlson comorbidity index and other information could not be available in the SEER database, which could also affect the quality of our results. Finally, no additional data of PC patients from other sources or institutions could be used for external verification, which might cause a selected bias.

Conclusion

No prognostic prediction model was widely accepted for PC patients so far. The results demonstrated that our nomogram model would be feasible and reliable, and we thought it could be helpful for clinicians to be faster and more accurately to evaluating the prognosis of PC patients. However, because of the limitations in our study, more prospective studies are needed to verify the accuracy of the nomogram.

Declarations

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AUTHORS' CONTRIBUTIONS

Yong-Bo Chen, Liang Gao and Ping-Hong You designed the study. Yong-Bo Chen and Liang-You Tang selected and analysed the data. Yong-Bo Chen, Jiang Guo and Yu-Chang Tian involved in statistical analysis. Yong-Bo Chen, Liang Gao, Liang-You Tang and Ping-Hong You drafted and revised the manuscript. All authors have reviewed and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The dataset supporting the conclusions of this study is available in the SEER database

ETHICS APPROVAL

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING OF INTERESTS

The authors declare that they have no conflict of interest.

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Figures

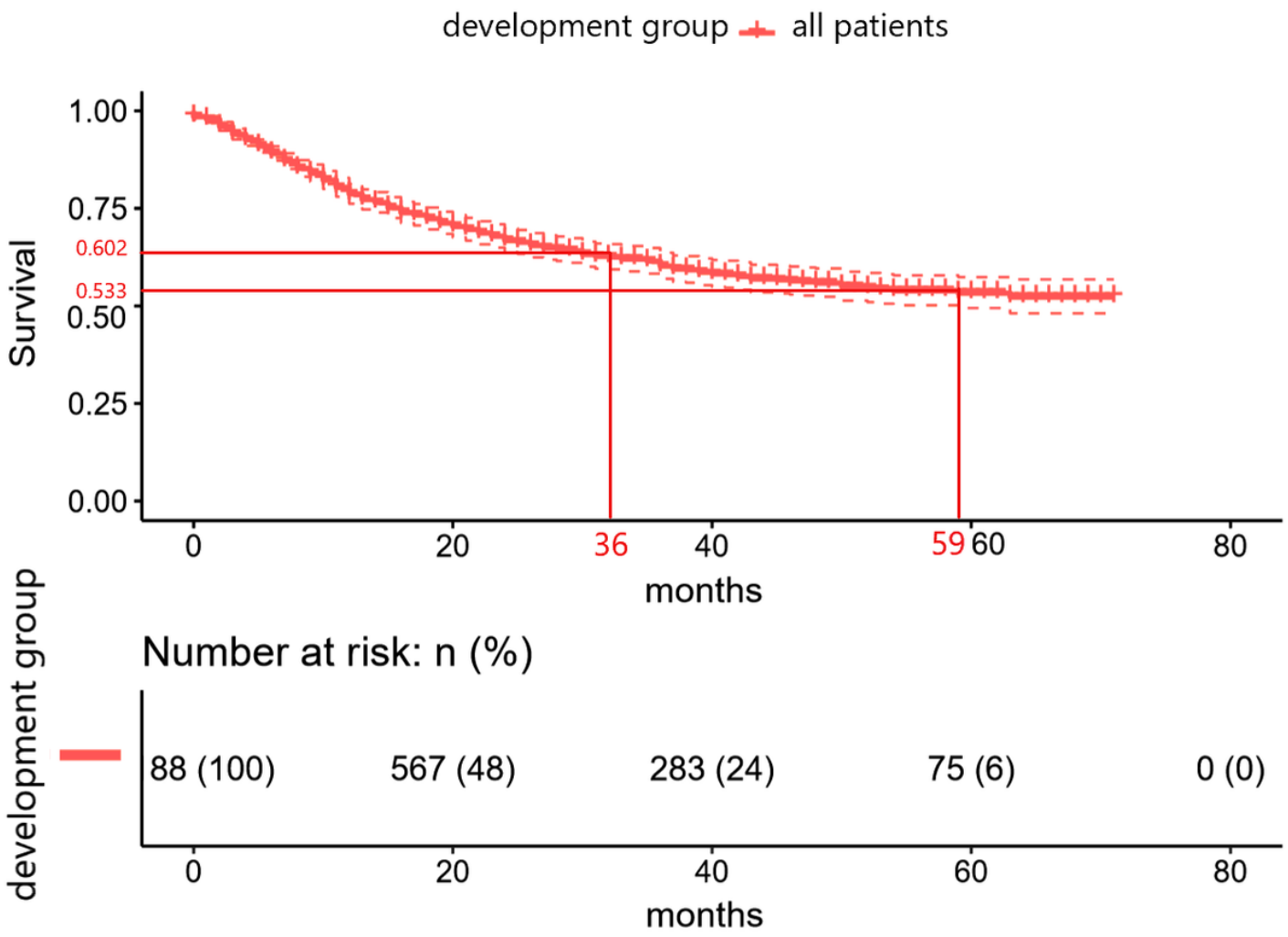

Figure 1

Figure 1

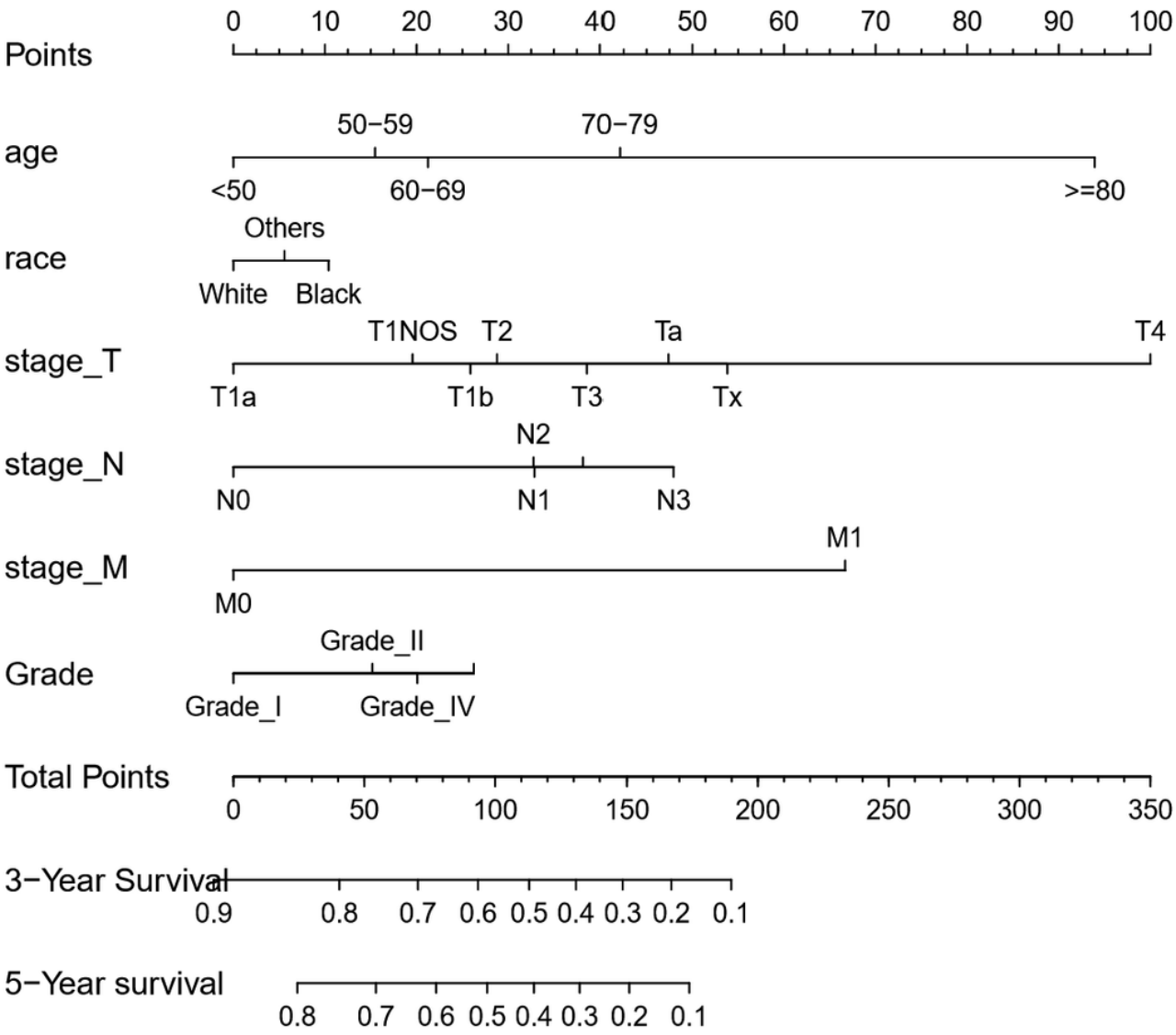

Figure 2

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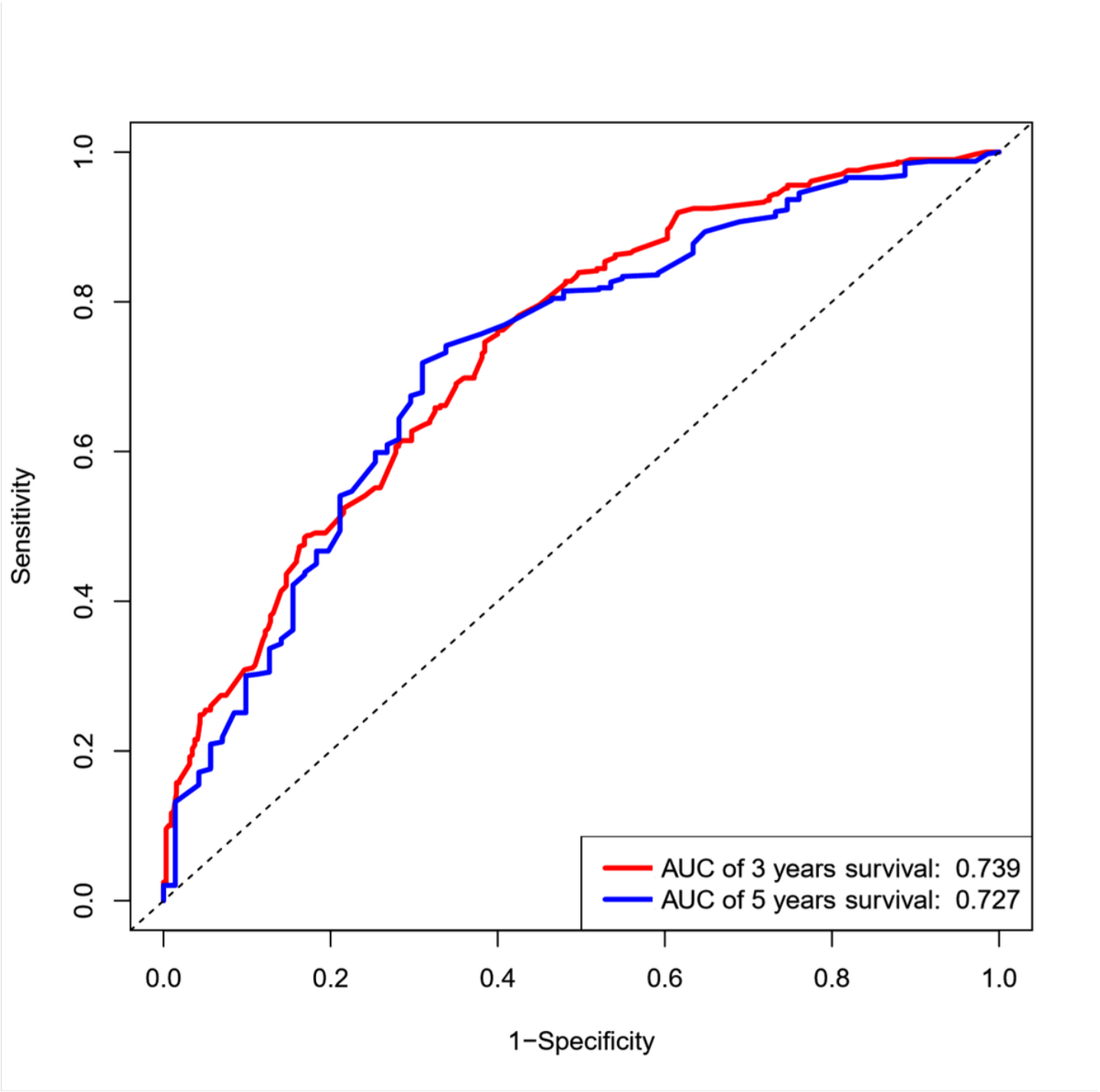

Figure 3

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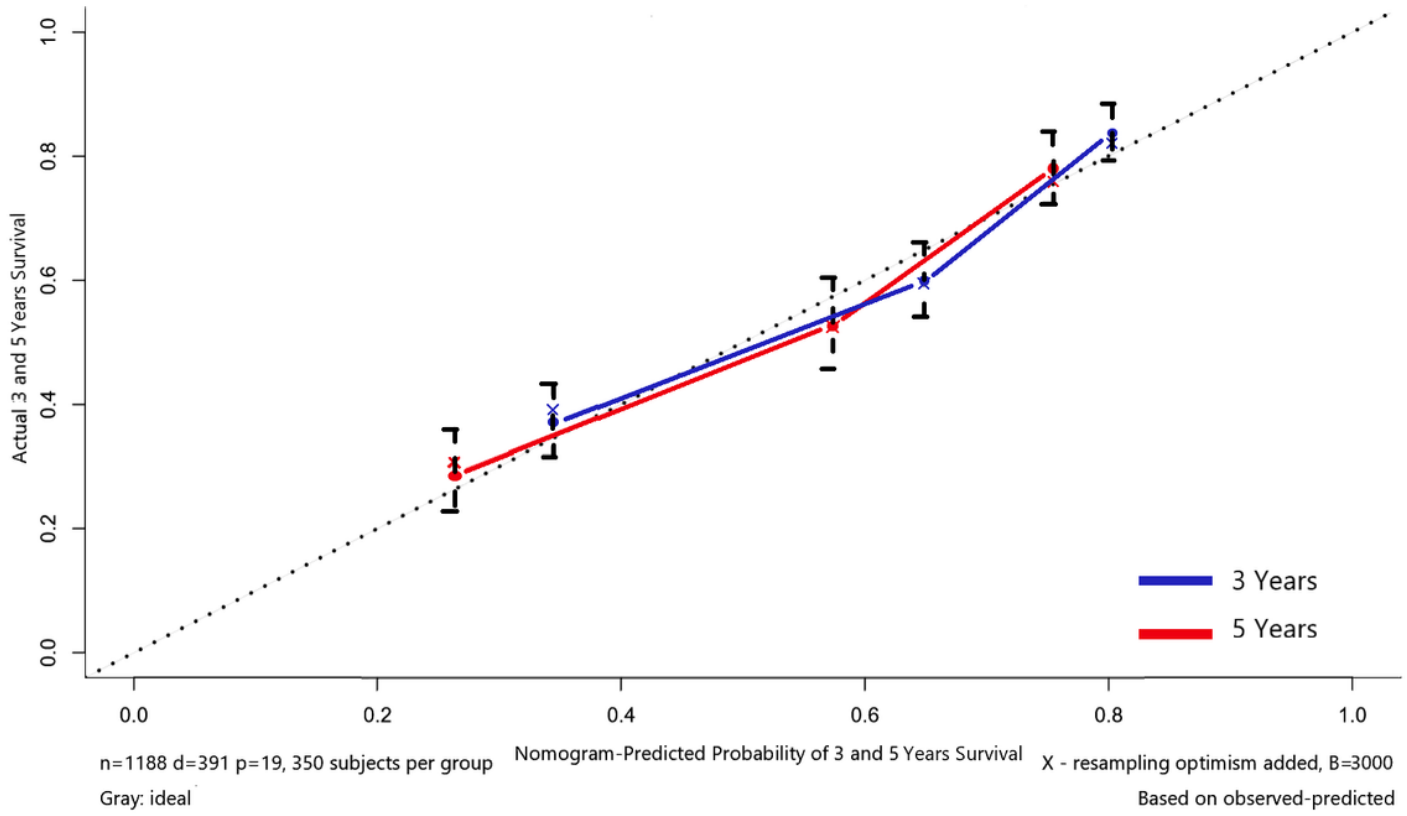

Figure 4

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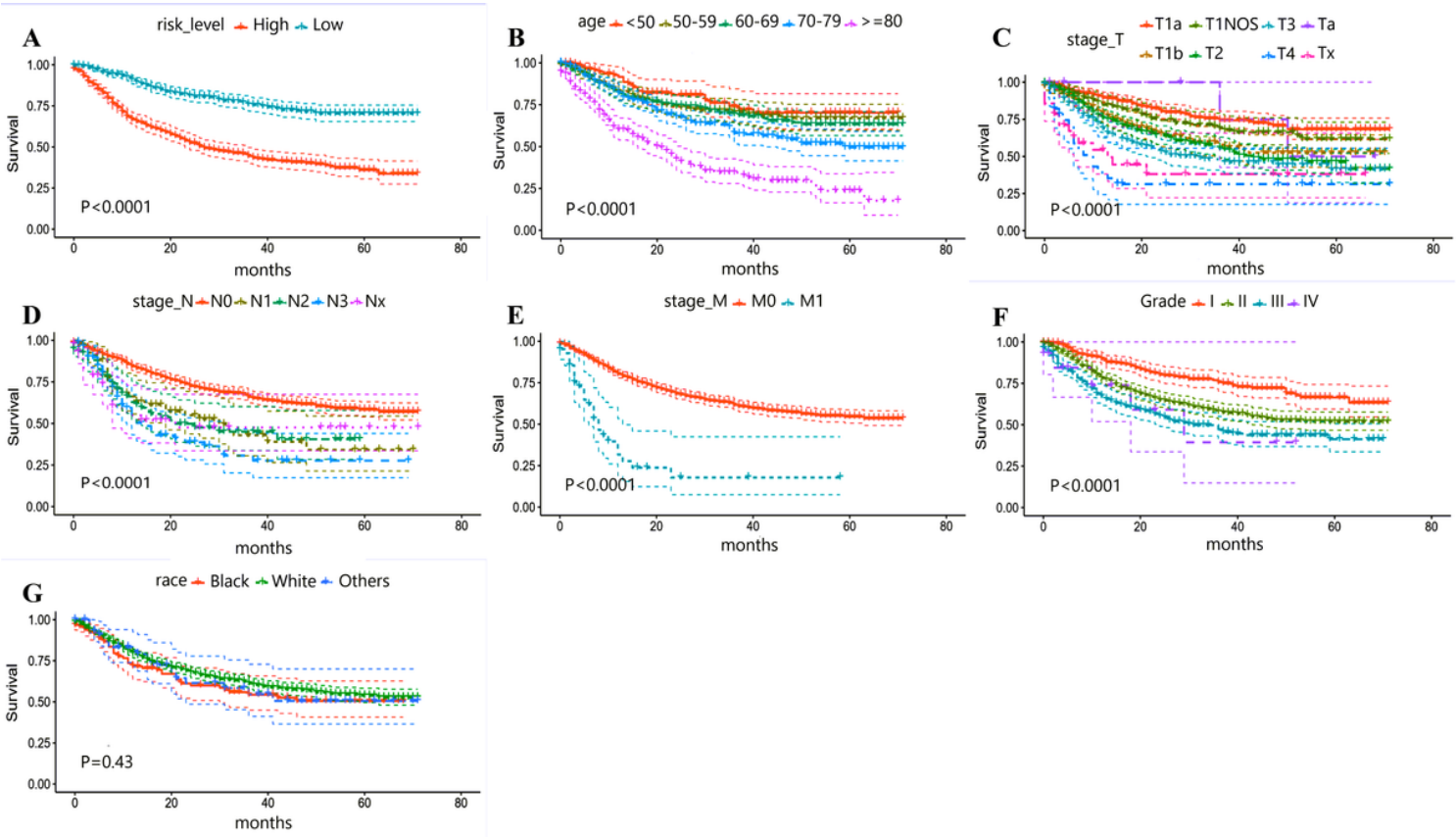

Figure 5

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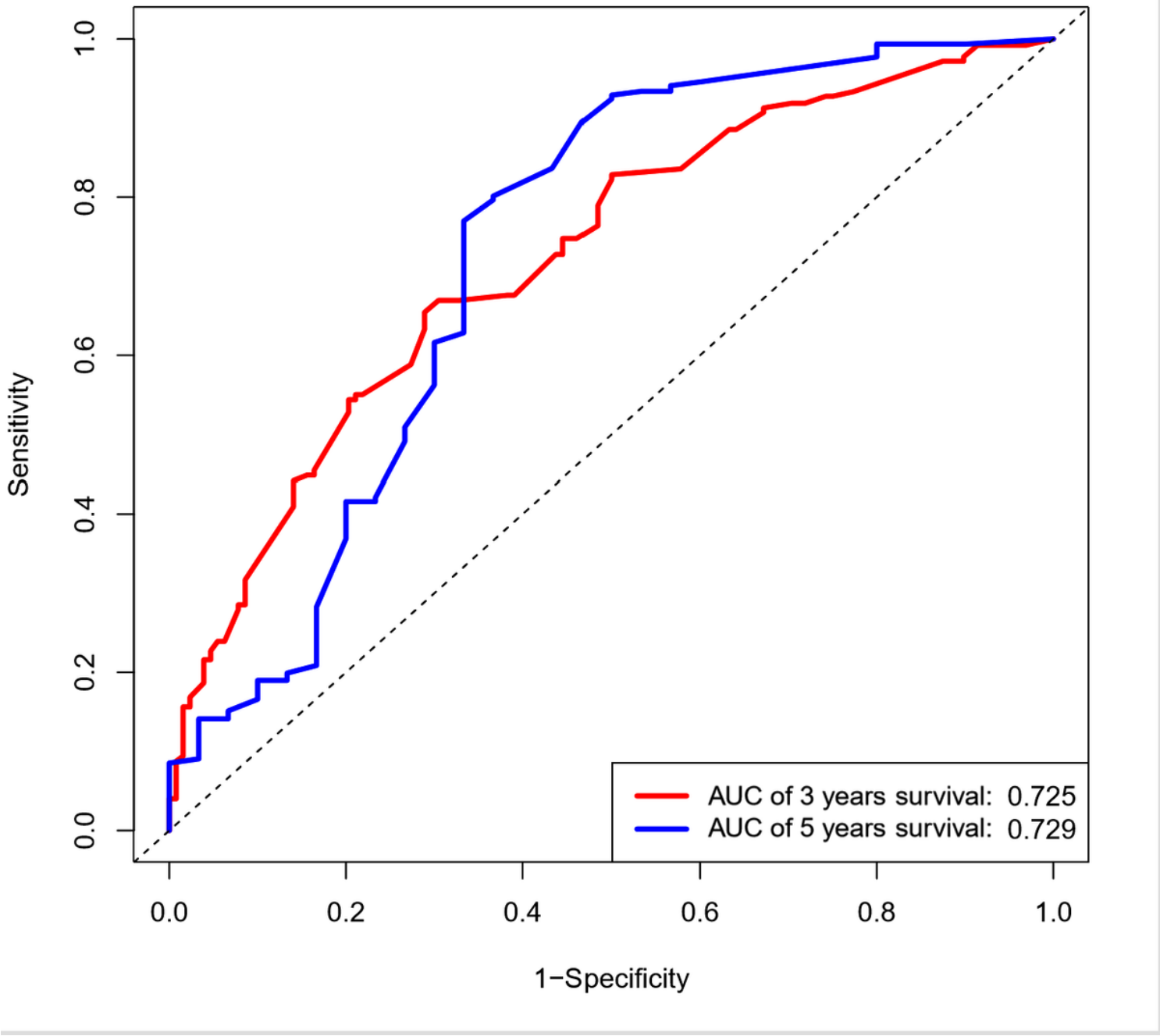

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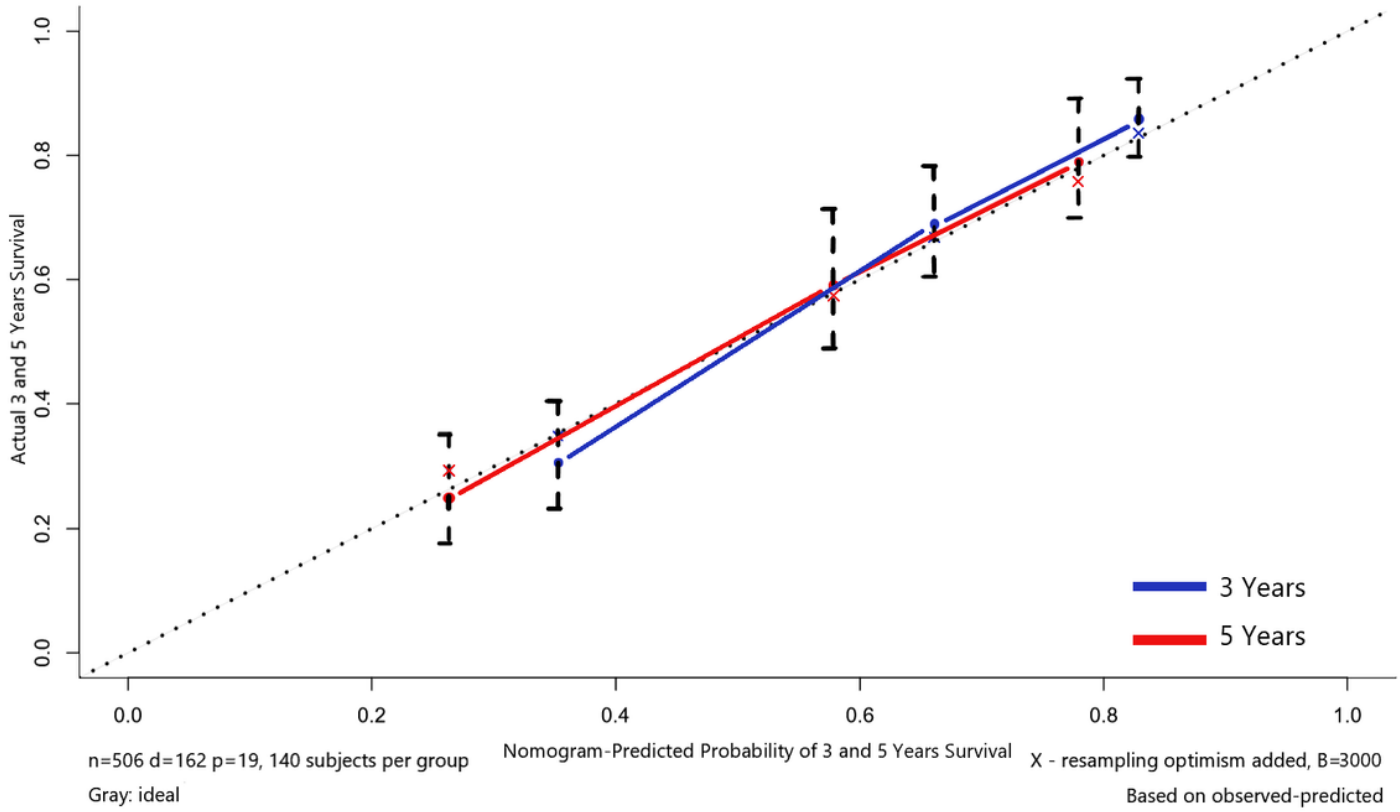

Figure 7

Figure 7