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A competing-risks nomogram for predicting cancer-specific death in upper-tract urothelial carcinoma: a population-based analysis

Running Head：Nomogram for UTUC cancer-specific death

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Abstract

Objectives: The purpose of this study is to use a competing-risks model to established a nomogram to more accurately analyze the prognostic factors for UTUC cancer-specific death (CSD).

Setting: The program has yielded a database of all cancer patients in 18 defined geographic regions of the United States.

Participants: We selected UTUC patients from the latest edition of the SEER database that covers from 1975 to 2016. After excluding patients with unknown histological grade, tumor size, and lymph node status, we finally selected 2576 patients.

Primary and secondary outcome measures: We used the Fine-Gray subdistribution proportional-hazards model for a multivariate analysis and compared the results with those obtained using Cox proportional-hazards models. We finally constructed a nomogram for the 3, 5, and 8 years CSD rates and tested these rates in a validation cohort.

Results: The subdistribution proportional-hazards model showed that sex, race, tumor size, distant metastasis, number of lymph nodes examined (LNE), and number of lymph nodes positive (LNP) were independent prognostic factors for CSD. The 3, 5, and 8 years C-indexes were 0.723, 0.707, and 0.696 in the training cohort, respectively, and 0.708, 0.702, and 0.701 in the validation cohort.

Conclusions: The competing-risks model showed that sex, race, tumor size, distant metastasis, LNE, and LNP were associated with CSD. The nomogram predicts the

probability of CSD in UTUC patients at 3, 5, and 8 years, which can improve the ability of clinicians to predict the survival probabilities in individual patients.

Strengths and limitations of this study:

- The study established the first competing risk nomogram for predicting the 3-, 5-, and 8-year specific mortality probability for UTUC based on a large retrospective sample, which can improve the ability of clinicians to predict the survival probabilities in individual patients.
- The established model is not comprehensive enough, because the SEER database does not include all prognostic factors for UTUC.
- The data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans.
- The model requires prospective studies to confirm its reliability.

Keywords: competing risk model, upper-tract urothelial carcinoma, nomogram, SEER, cancer-specific death

Introduction

Urothelial carcinomas are the fourth most common type of tumor,[1] and they can be located in the upper urinary tract or the lower. Upper-tract urothelial carcinoma (UTUC), which includes renal pelvis and ureter carcinoma, currently accounts for 5% of urothelial malignancies. [2] The annual incidence of UTUC is typically estimated

at 1 or 2 per 100,000 inhabitants in Western countries.[3] However, the increasing morbidity and mortality associated with UTUC[4, 5] are increasing the importance of this research.

A study showed that UTUC has unique prognostic factors, which are different from bladder cancer and other urinary tract cancers.[6] Most studies analyzing the prognostic factors for UTUC have adopted the Kaplan-Meier (K-M) method or Cox regression methods.[7–9] These methods analyze the overall cancer mortality rate when determining survival parameters while ignoring the possibility of bias caused by competing events. Competing events for cancer deaths refer to death from other causes not related to the primary cancer, such as other diseases, car collisions, and suicide. These factors are collectively classified as death events in traditional survival analysis, and they undoubtedly increase the calculated cancer mortality rate and hence can result in biased results. Applying standard survival analysis to competing-risks data leads to false and biased results.[10] Instead, the cumulative incidence function (CIF) of UTUC cancer-specific death (CSD) needs to be calculated and prognostic factors for UTUC analyzed using the Fine-Gray subdistribution proportional-hazards model.[11]

The purpose of our research is to identify the prognostic factors of UTUC and used them to construct a nomogram to predict the survival rates of patients at the 3, 5, and 8 years. A nomogram is based on a prognostic model and graphically presents the predictive abilities of different prognostic factors as the lengths of line segments. This format makes it easy for clinicians to make rapid and comprehensive judgments and

to predict the probability of CSD, which has great clinical significance. Some studies have constructed competing-risks nomograms for cancers such as sarcoma and prostate cancer,[12, 13] but research related to UTUC has been lacking.

The current study was conducted to assess the effect of several factors in UTUC using a competing-risks method, and to construct a comprehensive nomogram that presents the impacts of these prognostic factors in order to guide clinical work.

Methods

Database and patients

The Surveillance, Epidemiology, and End Results (SEER) program has yielded a database of all cancer patients in 18 defined geographic regions of the United States collected by the National Cancer Institute. It is the largest cancer registry in the United States and includes information on approximately 28% of the United States population. Because part of the SEER research data is publicly available, no informed consent or institutional review board approval is required when analyzing the data. We additionally requested chemotherapy data for inclusion in our research and obtained a license for using SEER software.[14, 15]

We selected UTUC patients from the latest edition of the SEER database that covers from 1975 to 2016. The primary sites were extracted using the SEER codes of "C65.9-Renal pelvis" and "C66.9-Ureter." We included all of the histological subtypes of UTUC, according to the ICD-O-3 (third revision of the International Classification of Diseases for Oncology). The following demographic indicators were selected: age at diagnosis, sex, race, and marital status. Primary site, histological

grade, tumor size, laterality, distant metastasis, surgery status, radiotherapy status, chemotherapy status, number of lymph nodes examined (LNE), lymph nodes positive (LNP), and lymph nodes ratio (LNR; calculated as the number of LNP divided by LNE) were also included as pathological characteristics. We divided the ages into four groups: 20–40, 40–60, 60–80, and >80 years. The tumor size was categorized into three groups: <2, 2–4, and ≥4 cm.[1, 16] The study outcomes included survival, CSD, and death due to other causes (DOC). The survival time was reported in the available data in months.

Exclusion criteria

Our preliminary selection of the above methods initially identified 13,581 patients. Then, in order to ensure the accuracy of the study, the exclusion criteria for the study data are as follows: unknown histological grade, unknown tumor size, and unknown lymph nodes status. The specific data selection process is shown in Figure 1. We finally chose 2576 patients for inclusion in follow-up investigations.

Figure 1

Statistical methods

We randomly divided the 2576 eligible patients into 2 groups using R software (version 3.5.3, The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org): 70% (n=1803) in the training cohort and 30% (n=773) in the validation cohort. We first described the basic composition of each factor in the two patient cohorts using SPSS software (version 23.0, Armonk, NY: IBM Corp). The LNR was expressed as median and interquartile-range values, while categorical

variables were represented as percentages.

In a univariate analysis, R software was used to calculate the CIF to describe the probability of death, while SAS software (SAS Institute, USA) was used to implement Gray's test to determine the difference in CIF between each variable group. We then performed a multivariate analysis using SAS. We used the Fine-Gray subdistribution proportional-hazards model for the multivariate analysis and compared the results with using traditional Cox proportional-hazards models. Applying the standard Cox regression method ignores the presence of competing risks and hence overestimates the actual incidence of beneficial events, and so may lead to inappropriate risk stratification.[17] Several studies have confirmed that different approaches can be used in competing-risks settings for multivariate survival analysis, but subdistribution proportional-hazards model have been found to be the best predictors of survival probability.[18]

Finally, the multivariate analysis results were used to construct a nomogram of the 3, 5, and 8 years CSD rates, which was tested using the validation cohort. We used the concordance index (C-index) and calibration plots to evaluate the differentiation ability and consistency of the established model.

All statistical tests were conducted using SPSS (version 23), R software (version 3.5.3), and SAS (version 9.4). Probability values of $P<0.05$ were considered statistically significant, and all tests were two-sided. The SEER database can be accessed free of charge, and this study was exempted from obtaining informed consent.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Patient characteristics

The composition of each variable for the 2576 patients in the training and validation cohorts is presented in Table 1. This table indicates that the largest proportions of the patients were aged 60–80 years (63.0% and 61.4% in the training and validation cohorts, respectively), male (both 59.6%), white (85.0% and 85.6%), and married (86.9% and 87.5%). The main UTUC sites were in the renal pelvis (64.4% and 61.6%, respectively, in the training and validation cohorts), with the rest in the ureter. Majority of patients were in the undifferentiated stage (56.8% and 58.7%), and most of the tumors in both cohorts were larger than 4 cm. Unilateral cases were distributed relatively uniformly, with the cancer on the left accounting for 55.6% in the training cohort, and 52.9% in the validation cohort. Most patients in both cohorts had received surgery, whereas a few patients had received radiotherapy or chemotherapy. Only about 9% of patients had distant metastasis. In the training and validation cohorts, LNE was mostly within the range of 1–3 (55.6% and 56.8%, respectively); the proportions of LNP were 36.0% and 33.1%, respectively; the

median LNRs were 0.00 (range, 0.00–0.46) and 0.00 (range, 0.00–0.36), respectively.

Table 1

Univariate analysis

We calculated the 3, 5, and 8 years cumulative incidence rates of CSD and DOC. Laterality and marital status were not related to either outcome (P>0.05), while sex, race, histological grade, chemotherapy status, LNP, and LNR were related to both outcomes (P<0.05). Age was significantly related to DOC, while primary site, tumor size, surgery status, radiotherapy status, distant metastasis, and LNE were significantly related to CSD. The CIF curves of variables specifically related to CSD are shown in Figure 2, while other figures are provided in Appendix 1. The cumulative incidence rates of CSD and DOC are compared in Table 2.

Figure 2, Table 2

Multivariate analysis

Our comparison of the competing-risks model with a traditional Cox regression model yielded the results presented in Table 3. The Cox regression model showed that tumor size, chemotherapy status, distant metastasis, and LNP were prognostic factors for UTUC (P<0.001). We then constructed the Fine-Gray subdistribution proportional-hazards model. The multivariate competing-risks analysis indicated that sex (hazard ratio [HR]=1.308 for female, 95% confidence interval [CI]=1.093–1.564), race (HR=1.670 for other races, 95% CI=1.290–2.162), tumor size (HR=1.656 for 2–4 cm, 95% CI=1.161–2.363; HR=2.065 for ≥4 cm, 95% CI=1.461–2.918), distant

metastasis (HR=2.233 for distant, 95% CI=1.706–2.923), LNE (HR=0.711 for 4–7 lymph nodes, 95% CI=0.545–0.928; HR=0.698 for ≥8 lymph nodes, 95% CI=0.540–0.903), and LNP (HR=2.252, 95% CI=1.580–3.211) were prognostic factors affecting UTUC, as presented in Table 3.

Table 3

Construction and verification of the nomogram

Figure 3 shows the nomogram we constructed according to the results of the multivariate competing-risks analysis for predicting the CSD probabilities at 3, 5, and 8 years. The figure shows that LNP had the greatest impact on the probability of CSD, followed by distant metastasis, tumor size, race, LNE, and sex.

We used the validation cohort to verify the nomogram after establishing it. The 3, 5, and 8 years C-indexes were 0.723, 0.707, and 0.696 for the training cohort, respectively, and 0.708, 0.702, and 0.701 for the validation cohort. All of these values exceed 0.6, which indicates that the model has good discrimination ability. We then tested the prediction accuracy of the model. As shown in Figure 4, the 3, 5, and 8 years calibration plots for both cohorts were very close to the standard straight line, demonstrating that the model was well calibrated.

Figures 3, 4

Discussion

The increasing incidence of UTUC[19] makes it necessary to further explore the

prognostic factors for UTUC. The present study used a competing-risks model to more accurately explore the prognostic factors for UTUC, and used these factors to construct a nomogram to provide clinicians with direct guidance when they are making relevant predictions.

The application of study criteria resulted in the inclusion in 2576 patients from the SEER database, and 1542 of these patients died during the follow-up, although only 750 of the deaths were related to UTUC. This means that the number of DOC patients was almost the same as that for CSD. In this situation, if the traditional K-M or Cox survival analysis had been adopted, both death outcomes would have been considered to be related to UTUC.[20, 21] This would overestimate the proportion of CSD patients and hence not truly reflect the prognosis of CSD. We overcame this shortcoming by using a subdistribution proportional-hazards model, which can properly address the situation where the available data are related to multiple potential outcomes.[22] This method was first proposed by Fine and Gray, and has also been applied in some previous studies.[23–25] In the presence of competing risks, we used the CIF and the subdistribution proportional-hazards model to explore the impact of various factors on CSD.

The univariate analysis results showed that sex, race, primary site, histological grade, tumor size, surgery status, radiotherapy status, chemotherapy status, distant metastasis, LNE, LNP, and LNR are influencing factors for CSD, while age, sex, race, histological grade, chemotherapy status, LNP, and LNR are influencing factors for DOC. The multivariate Cox regression model results showed that tumor size, distant

metastasis, chemotherapy status, and LNP are prognostic factors for CSD. The subdistribution proportional-hazards model showed that sex, race, tumor size, distant metastasis, LNE, and LNP are independent prognostic factors for CSD.

Age is a prognostic factor for most cancers, and this has also found to be the case for CSD.[26, 27] However, our univariate analysis results showed that age is only a prognosis factor for DOC, and the multivariate analysis did not include age as a variable, indicating that age is not a separate prognosis factor for UTUC. Previous studies may have ignored competing events, and sex and race have always been controversial prognostic factors. One study showed that age and race are preoperative prognostic factors for UTUC patients.[28] In contrast, another study found no statistically significant differences in survival between males and females.[29] The competing-risks model in our study showed that sex and race are risk factors for UTUC. However, since most of the patients included in the SEER database are white, the results regarding race need to be further validated.

Tumor size has always been a prognostic factor. One study found 5-year recurrence-free survival rates for patients with tumor sizes <3 cm and ≥3 cm of 46.9% and 25.8%, respectively.[30] The univariate and multivariate analyses performed in the present study indicated that tumor size is an influencing factor for CSD, with the prognosis being worse for tumors larger than 2 cm. In terms of treatment methods, surgery status, radiotherapy status, and chemotherapy status were not influencing factors for CSD in the subdistribution proportional-hazards model. This conflicts with some previous findings,[31–33] suggesting that traditional Cox regression analysis

overestimates the effects of surgery, radiotherapy, and chemotherapy. Of course, the relative lack of information on the radiotherapy status and chemotherapy status in the SEER database may also lead to inaccurate results, and so further exploration of these indicators is needed.

Some indicators related to lymph nodes (e.g., distant lymph node metastasis, LNP, and LNE) have been found to be important clinical information for the prognosis of cancer, but whether they are independent prognostic factors for UTUC has not been determined. One study found that lymph node metastases were significantly associated with reduced disease-specific survival in univariate analysis.[34] Our research also found that distant metastasis is an important prognostic factor for CSD, in both the univariate and multivariate analyses.

It is worth noting that very few studies have investigated LNP, LNE, and LNR. Our study is the first to use the SEER database to analyze the prognostic impact of these indicators on UTUC, and the results may be more accurate than those of studies involving small samples. LNR is an emerging indicator that has been regarded as a prognostic factor in rectal cancer and breast cancer.[35, 36] We found that LNR was an influencing factor for UTUC in the univariate analysis but not in the multivariate analysis. Moreover, both LNE and LNP entered the subdistribution proportional-hazards model, which showed that after adjusting for the effects of LNE and LNP, LNR was no longer an independent prognostic indicator. After excluding competing events, LNE was an independent prognostic factor for UTUC. It can be seen from the results that a higher LNE decreases the probability of CSD. However,

LNE did not influence DOC. This shows that LNE is more specific for UTUC, and so more attention should be paid to its role as a prognostic factor for UTUC patients in the future. LNP was a prognostic factor in all of the analyses, indicating that it greatly influences the prognosis of UTUC.

We utilized the results from the above-mentioned subdistribution proportional-hazards model to construct a nomogram that graphically presents the degrees of influence of various prognostic factors. This nomogram also integrates various indicators to predict the 3, 5, and 8 years probabilities of CSD. The C-indexes for the nomogram all exceeded 0.6, demonstrating that the model provides a good fit to the available data. The prediction calibration curves in Figure 4 are very close to the standard curve, which indicates that the nomogram has good predictive ability. The results for the validation cohort also show that the model is stable. This model can therefore help clinicians to quickly and easily determine the prognosis of individual patients and provide guidance in their clinical decision-making. However, the stability of the model needs further verification.

Inevitably, our research had some limitations. First, the established model is not comprehensive enough, because the SEER database does not include all prognostic factors for UTUC. Second, the data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans. Finally, the model requires prospective studies to confirm its reliability.

5. Conclusions

In summary, this study used a competing-risks model to determine the prognostic

factors for UTUC. The subdistribution proportional-hazards model showed that sex, race, tumor size, distant metastasis, LNE, and LNP were associated with CSD, while LNR was not. The constructed nomogram can predict the 3, 5, and 8 years CSD probabilities of patients based on these relevant factors, which can support clinicians to make better judgments of the survival rates of individual patients.

Footnotes

Contributorship statement: JL, CZL, and XL designed the study; QH, FFZ, and XJF collected and analyzed the data; CZL and XL drafted the initial manuscript; DDH, FSX, and SZ reviewed and edited the article; All authors read and approved the final manuscript.

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Availability of data and materials: Ethical approval was waived, and informed consent was unnecessary because the SEER research data are anonymous and publicly available.

Patient consent for publication: Not required.

Data availability statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1 The basic characteristics of the patients in this study.

Variable	Training Cohort	Validation Cohort
Number of Patients n (%)	1803(70)	773(30)
Age of diagnosis n (%)		
20-39	8(0.4)	5(0.6)
40-59	270(15.0)	130(16.8)
60-79	1135(63.0)	475(61.4)
≥80	390(21.6)	163(21.1)
Sex n (%)		
Male	1075(59.6)	461(59.6)
Female	728(40.4)	312(40.4)
Race n (%)		
White	1532(85.0)	662(85.6)
Black	95(5.3)	35(4.5)
Other	176(9.8)	76(9.8)
Marital status n (%)		
Married	1566(86.9)	676(87.5)
Single	166(9.2)	70(9.1)
Others	71(3.9)	27(3.5)
Site n (%)		
Renal pelvis	1161(64.4)	476(61.6)
Ureter	642(35.6)	297(38.4)
Grade n (%)		
Well	50(2.8)	13(1.7)
Moderate	145(8.0)	73(9.4)
Poor	584(32.4)	233(30.1)
Undifferential	1024(56.8)	454(58.7)
Size n (%)		
<2	254(14.1)	114(14.7)
[2,4)	584(32.4)	243(31.4)
≥4	965(53.5)	416(53.8)
Laterality n (%)		
Left	1002(55.6)	409(52.9)
Right	801(44.4)	364(47.1)
Surgery n (%)		
Yes	1791(99.3)	768(99.4)
NO/Unknown	12(0.7)	5(0.6)
Radiotherapy n (%)		
Yes	134(7.4)	46(6.0)
NO/Unknown	1669(92.6)	727(94.0)
Chemotherapy n (%)		
Yes	566(31.4)	236(30.5)

NO/Unknown	1237(68.6)	537(69.5)
Distant metastasis n (%)		
No	1638(90.8)	703(90.9)
Yes	165(9.2)	70(9.1)
LNE n (%)		
1-3	1003(55.6)	439(56.8)
4-7	343(19.0)	164(21.2)
≥8	457(25.3)	170(22.0)
LNP n (%)		
No	1154(64.0)	517(66.9)
Yes	649(36.0)	256(33.1)
LNR n (%)	0.00(0.00-0.46)	0.00(0.00-0.36)

Table 2 The cumulative incidences of CSD and DOC among patients with UTUC.

Variables	Cancer-specific death (%)				Death due to other causes (%)			
	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	*P*	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	*P*
Age				0.368				<0.001
20-39	16.667 (13.333-20.000)	33.333 (29.065-37.602)	-		-	-	-	
40-59	31.794 (31.199-32.388)	34.798 (34.180-35.415)	36.661 (36.025-37.298)		9.094 (8.731-9.458)	14.705 (14.231-15.178)	19.845 (19.278-20.412)	
60-79	24.599 (24.334-24.865)	29.482 (29.189-29.775)	32.246 (31.930-32.563)		21.973 (21.716-22.229)	28.879 (28.582-29.175)	34.133 (33.794-34.471)	
⩾80	28.461 (27.991-28.931)	32.050 (31.552-32.548)	34.019 (33.499-34.540)		35.067 (34.566-35.569)	42.984 (42.445-43.524)	53.563 (52.972-54.153)	
Sex				<0.001				<0.001
Male	23.573 (23.303-23.843)	27.370 (27.078-27.662)	30.109 (29.794-30.424)		25.258 (24.982-25.535)	33.576 (33.258-33.893)	40.036 (39.680-40.393)	
Female	30.823 (30.469-31.177)	35.953 (35.572-36.334)	37.895 (37.499-38.292)		19.189 (18.886-19.492)	24.057 (23.715-24.398)	30.607 (30.198-31.016)	
Race				<0.001				<0.001
White	24.930 (24.701-25.158)	28.718 (28.472-28.964)	30.774 (30.513-31.035)		24.031 (23.804-24.259)	31.338 (31.079-31.597)	38.267 (37.969-38.565)	
Black	27.787 (26.808-28.766)	37.875 (36.772-38.978)	43.315 (42.144-44.486)		21.152 (20.279-22.025)	25.483 (24.524-26.442)	27.433 (26.420-28.446)	
Other	39.718 (38.935-40.500)	45.609 (44.784-46.435)	49.063 (48.199-49.926)		12.901 (12.372-13.431)	17.675 (17.046-18.303)	23.038 (22.291-23.786)	
Marital status				0.531				0.355
Married	26.477	30.515	32.943		22.980	29.955	36.394	

	(26.245-26.708)	(30.267-30.764)	(32.678-33.207)		(22.759-23.202)	(29.702-30.207)	(36.104-36.684)	
Single	27.825 (27.105-28.544)	34.957 (34.148-35.766)	38.136 (37.289-38.984)		19.018 (18.387-19.648)	25.826 (25.087-26.565)	32.010 (31.153-32.868)	
Others	24.022 (22.916-25.129)	28.842 (27.608-30.076)	28.842 (27.608-30.076)		28.182 (27.029-29.335)	33.171 (31.893-34.450)	42.216 (40.728-43.704)	
Site				<0.001				0.210
Renal pelvis	30.419 (30.141-30.698)	34.855 (34.558-35.151)	37.540 (37.227-37.852)		22.712 (22.458-22.966)	28.631 (28.346-28.915)	34.427 (34.103-34.751)	
Ureter	19.306 (18.978-19.634)	23.420 (23.053-23.788)	25.261 (24.867-25.654)		23.014 (22.662-23.365)	31.767 (31.352-32.182)	39.588 (39.107-40.070)	
Grade				<0.001				0.047
Well	10.783 (9.858-11.708)	10.783 (9.858-11.708)	14.410 (13.262-15.558)		15.456 (14.364-16.549)	23.935 (22.568-25.301)	40.376 (38.543-42.210)	
Moderate	11.662 (11.110-12.214)	14.471 (13.847-15.094)	17.975 (17.254-18.695)		10.494 (9.960-11.029)	16.779 (16.100-17.458)	28.067 (27.142-28.992)	
Poor	28.630 (28.249-29.012)	32.995 (32.590-33.399)	34.980 (34.560-35.399)		24.378 (24.016-24.740)	31.083 (30.679-31.487)	36.517 (36.077-36.957)	
Undifferential	28.159 (27.863-28.455)	33.075 (32.751-33.398)	35.658 (35.308-36.008)		24.112 (23.830-24.395)	31.206 (30.882-31.531)	37.198 (36.817-37.580)	
Size				<0.001				0.377
<2	10.662 (10.246-11.078)	14.382 (13.884-14.881)	18.333 (17.72-18.945)		24.122 (23.544-24.699)	31.144 (30.482-31.806)	41.534 (40.717-42.352)	
[2,4)	20.400 (20.050-20.750)	26.809 (26.406-27.212)	29.821 (29.383-30.260)		20.624 (20.272-20.976)	27.885 (27.471-28.298)	35.394 (34.898-35.890)	
⩾4	34.237 (33.923-34.552)	37.483 (37.155-37.810)	39.206 (38.868-39.544)		23.801 (23.519-24.083)	30.424 (30.107-30.741)	35.440 (35.091-35.789)	

Laterality				0.896				0.635
Left	26.117 (25.828-26.405)	31.350 (31.034-31.667)	33.726 (33.391-34.062)		24.117 (23.836-24.399)	30.669 (30.353-30.986)	35.750 (35.394-36.106)	
Right	26.973 (26.647-27.298)	30.190 (29.846-30.535)	32.640 (32.274-33.006)		21.157 (20.857-21.457)	28.446 (28.096-28.797)	36.696 (36.283-37.108)	
Surgery				0.029				0.132
Yes	26.232 (26.016-26.447)	30.613 (30.380-30.846)	33.048 (32.800-33.296)		22.666 (22.460-22.872)	29.620 (29.384-29.856)	36.174 (35.903-36.445)	
NO/Unknown	58.333 (54.877-61.790)	-	-		41.667 (38.639-44.695)	-	-	
Radiotherapy				<0.001				0.940
Yes	42.957 (42.073-43.841)	47.953 (47.041-48.865)	49.418 (48.485-50.351)		26.414 (25.633-27.196)	32.064 (31.216-32.911)	34.468 (33.584-35.351)	
NO/Unknown	25.142 (24.922-25.363)	29.398 (29.159-29.637)	31.898 (31.643-32.154)		22.510 (22.297-22.723)	29.506 (29.261-29.750)	36.371 (36.087-36.654)	
Chemotherapy				<0.001				0.007
Yes	35.840 (35.412-36.268)	41.411 (40.954-41.868)	44.178 (43.698-44.658)		20.103 (19.747-20.459)	26.626 (26.209-27.042)	31.696 (31.233-32.159)	
NO/Unknown	22.389 (22.145-22.633)	26.245 (25.980-26.510)	28.493 (28.210-28.776)		24.052 (23.800-24.303)	31.128 (30.844-31.413)	38.226 (37.896-38.556)	
Distant metastasis				<0.001				0.905
No	22.843 (22.627-23.059)	27.444 (27.206-27.682)	29.995 (29.740-30.251)		22.251 (22.036-22.465)	29.517 (29.270-29.765)	36.603 (36.316-36.891)	
Yes	62.766 (61.998-63.533)	64.400 (63.634-65.167)	65.218 (64.451-65.984)		28.317 (27.603-29.032)	31.513 (30.767-32.258)	32.330 (31.577-33.083)	

LNE			0.002				0.699
1-3	29.182 (28.887-29.478)	34.316 (33.998-34.633)	36.877 (36.544-37.210)	21.861 (21.592-22.130)	29.193 (28.884-29.501)	36.619 (36.264-36.974)	
4-7	22.696 (22.224-23.168)	26.540 (26.019-27.061)	28.034 (27.481-28.588)	26.331 (25.828-26.835)	30.175 (29.629-30.720)	35.705 (35.077-36.333)	
⩾8	23.311 (22.893-23.728)	26.017 (25.572-26.462)	28.677 (28.189-29.165)	22.268 (21.859-22.678)	30.242 (29.759-30.725)	34.775 (34.235-35.315)	
LNP			<0.001				0.009
No	16.502 (16.273-16.731)	21.003 (20.741-21.264)	23.860 (23.571-24.148)	18.979 (18.738-19.221)	27.239 (26.948-27.531)	35.417 (35.069-35.765)	
Yes	44.145 (43.743-44.546)	48.231 (47.817-48.645)	49.950 (49.523-50.376)	29.565 (29.196-29.934)	34.071 (33.676-34.465)	37.613 (37.190-38.037)	
LNR			<0.001				<0.001

Table 3 Selected variables by proportional subdistribution hazard model and multivariate Cox regression model.

Variables	Proportional subdistribution hazards model				Cox regression model			
	Coefficient	HR	95%CI	*P*	Coefficient	HR	95%CI	*P*
Age								
20-39		Reference				Reference		
40-59	0.003	0.970	0.321-2.933	0.957	0.356	1.531	0.378-6.205	0.551
60-79	0.071	0.862	0.289-2.574	0.791	1.206	2.181	0.524-8.773	0.272
⩾80	0.003	0.968	0.321-2.922	0.954	3.302	3.646	0.903-14.718	0.069
Sex								
Male		Reference				Reference		
Female	8.612	1.308	1.093-1.564	0.003	1.108	0.935	0.825-1.060	0.293
Race								
White		Reference				Reference		
Black	0.502	1.147	0.785-1.675	0.479	2.535	1.243	0.951-1.625	0.111
Other	15.138	1.670	1.290-2.162	<0.001	0.007	0.991	0.809-1.214	0.932
Marital status								
Married		Reference				Reference		
Single	0.828	1.147	0.853-1.543	0.363	0.802	1.101	0.892-1.359	0.370
Others	0.203	0.902	0.576-1.412	0.652	0.066	0.960	0.702-1.313	0.797
Site								
Renal pelvis		Reference				Reference		
Ureter	2.831	0.837	0.680-1.030	0.092	0.172	0.971	0.846-1.115	0.678
Grade								
Well		Reference				Reference		
Moderate	0.005	1.033	0.416-2.566	0.944	0.770	0.798	0.482-1.321	0.380

Poor	2.172	1.848	0.817-4.181	0.141	3.700	1.546	0.992-2.409	0.054
Undifferential	2.535	1.929	0.859-4.330	0.111	3.630	1.534	0.988-2.383	0.057
Size								
<2		Reference				Reference		
2-4	7.735	1.656	1.161-2.363	0.005	1.161	1.127	0.907-1.400	0.281
⩾4	16.867	2.065	1.461-2.918	<0.001	17.071	1.548	1.258-1.905	<0.001
Laterality								
Left		Reference				Reference		
Right	0.833	1.087	0.908-1.301	0.362	0.098	1.020	0.903-1.152	0.754
Surgery								
Yes		Reference				Reference		
NO/Unknown	0.415	1.310	0.576-2.976	0.519	1.851	1.502	0.836-2.698	0.174
Radiotherapy								
Yes		Reference				Reference		
NO/Unknown	0.766	0.874	0.646-1.182	0.382	2.956	0.831	0.674-1.026	0.086
Chemotherapy								
Yes		Reference				Reference		
NO/Unknown	0.052	0.975	0.786-1.210	0.820	15.710	1.348	1.163-1.562	<0.001
Distant metastasis								
No		Reference				Reference		
Yes	34.221	2.233	1.706-2.923	<0.001	107.712	2.729	2.258-3.298	<0.001
LNE								
1-3		Reference				Reference		
4-7	6.317	0.711	0.545-0.928	0.012	0.518	0.939	0.791-1.115	0.472
⩾8	7.517	0.698	0.540-0.903	0.006	3.203	0.856	0.722-1.015	0.074
LNP								

No		Reference				Reference		
Yes	20.122	2.252	1.580-3.211	<0.001	48.506	2.365	1.856-3.013	<0.001
LNR	0.033	0.963	0.638-1.452	0.856	0.086	1.043	0.785-1.387	0.769

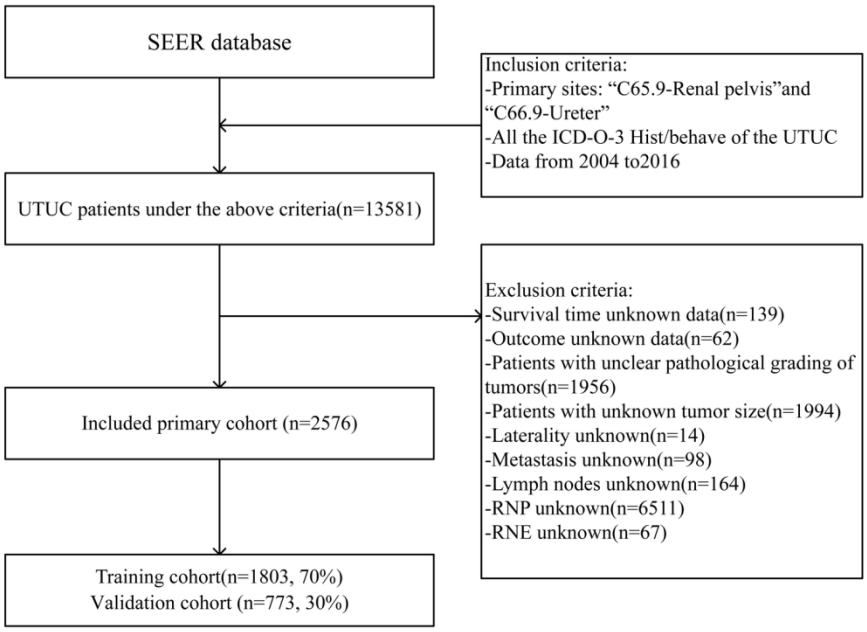
Figure legends

Figure 1. Data selection flowchart.

Figure 2. The CIF curves of UTUC cancer-specific death (CSD). Site, size, surgery, radiotherapy, distant metastasis, and LNE were significantly related to the patients of CSD. LNE: lymph nodes examined.

Figure 3. Nomogram based on the competing risk analysis to predict cancer-specific death probabilities at 3, 5, and 8 years for UTUC patients.

Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years calibration plots of the training (A, C, E) and validation (B, D, F) cohort.



Data selection flowchart.

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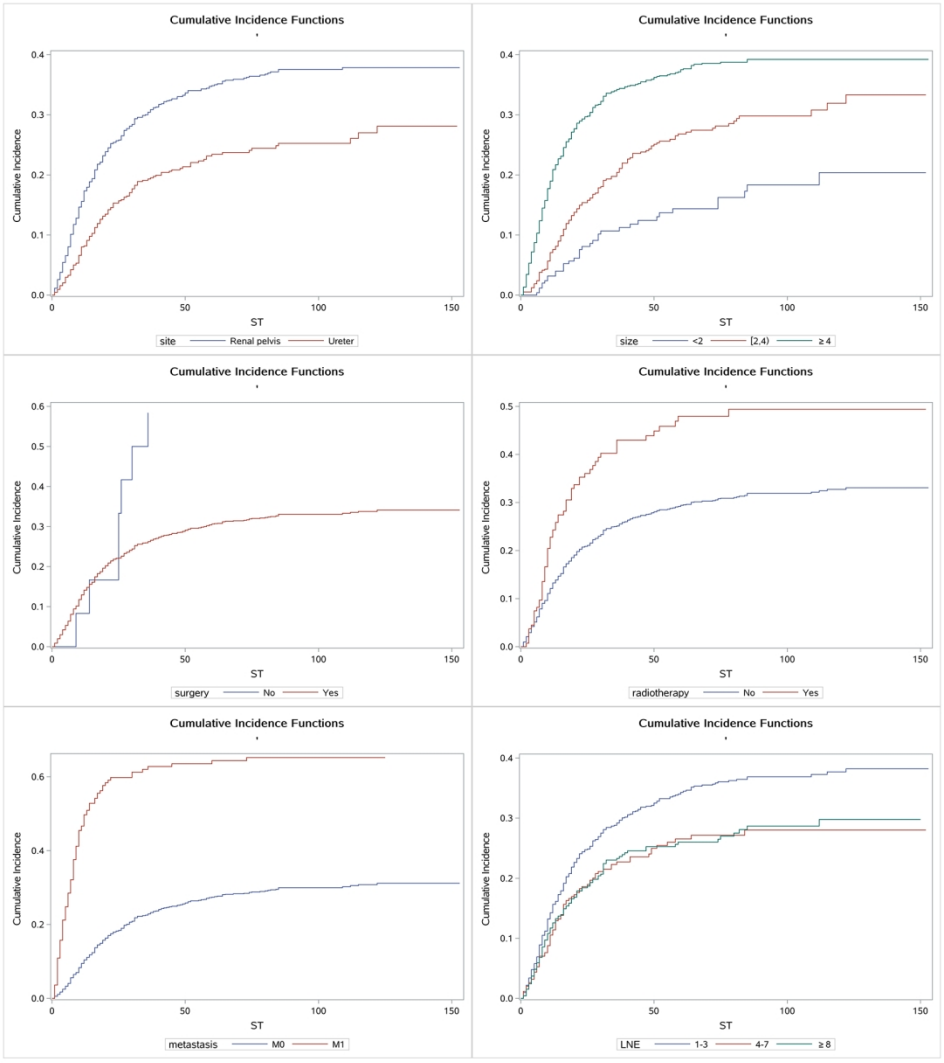
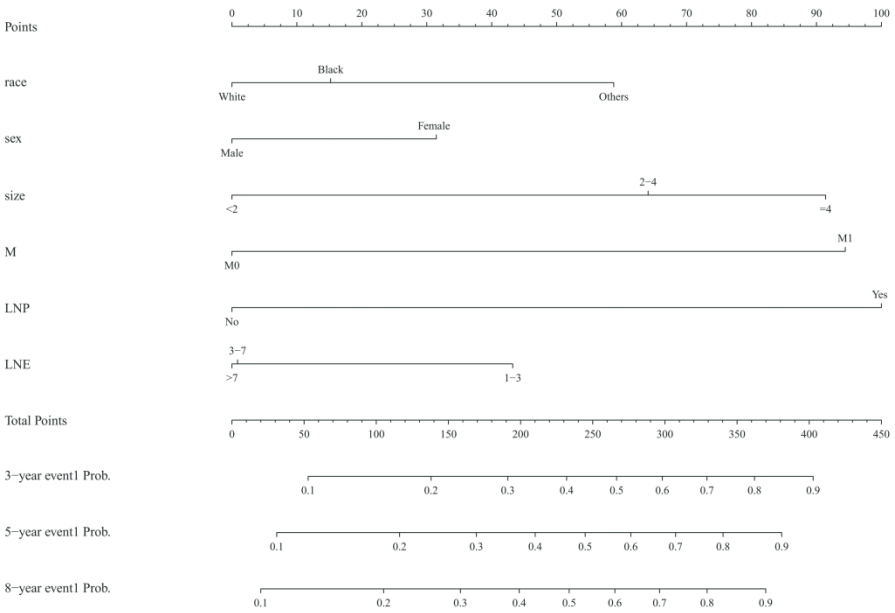


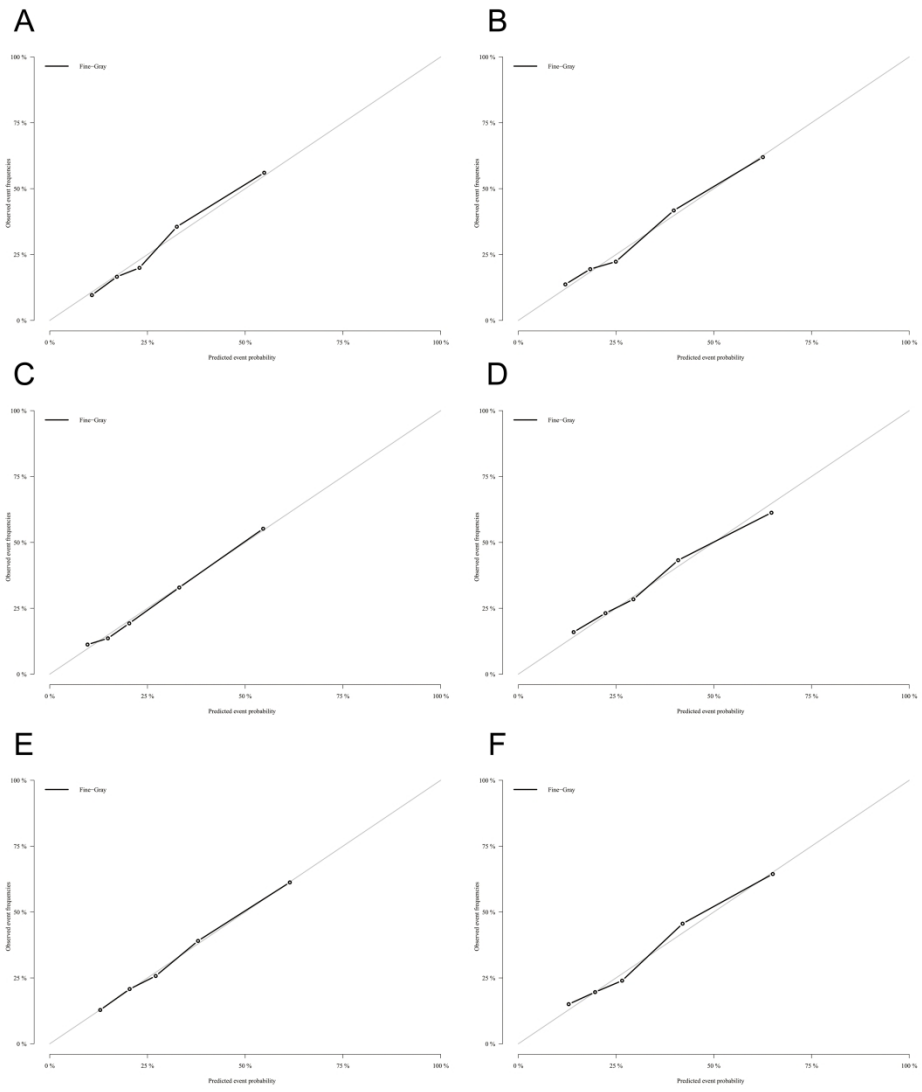
The CIF curves of UTUC cancer-specific death (CSD). Site, size, surgery, radiotherapy, distant metastasis, and LNE were significantly related to the patients of CSD. LNE: lymph nodes examined.

160x178mm (300 x 300 DPI)



Nomogram based on the competing risk analysis to predict cancer-specific death probabilities at 3, 5, and 8 years for UTUC patients.

149x113mm (600 x 600 DPI)



Calibration curves. Calibration curves for 3, 5, and 8 years calibration plots of the training (A, C, E) and validation (B, D, F) cohort.

159x180mm (600 x 600 DPI)

Figure 1

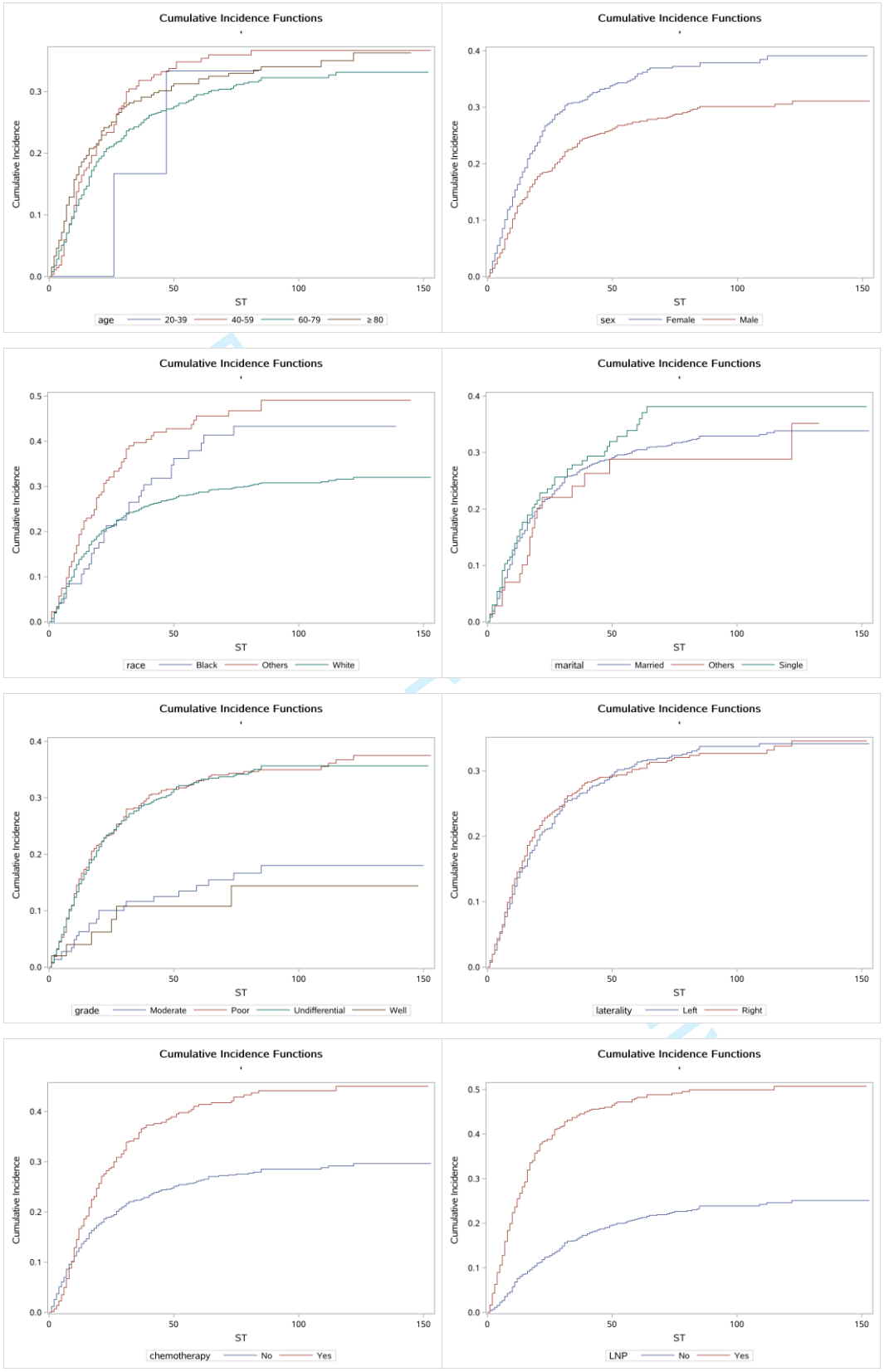
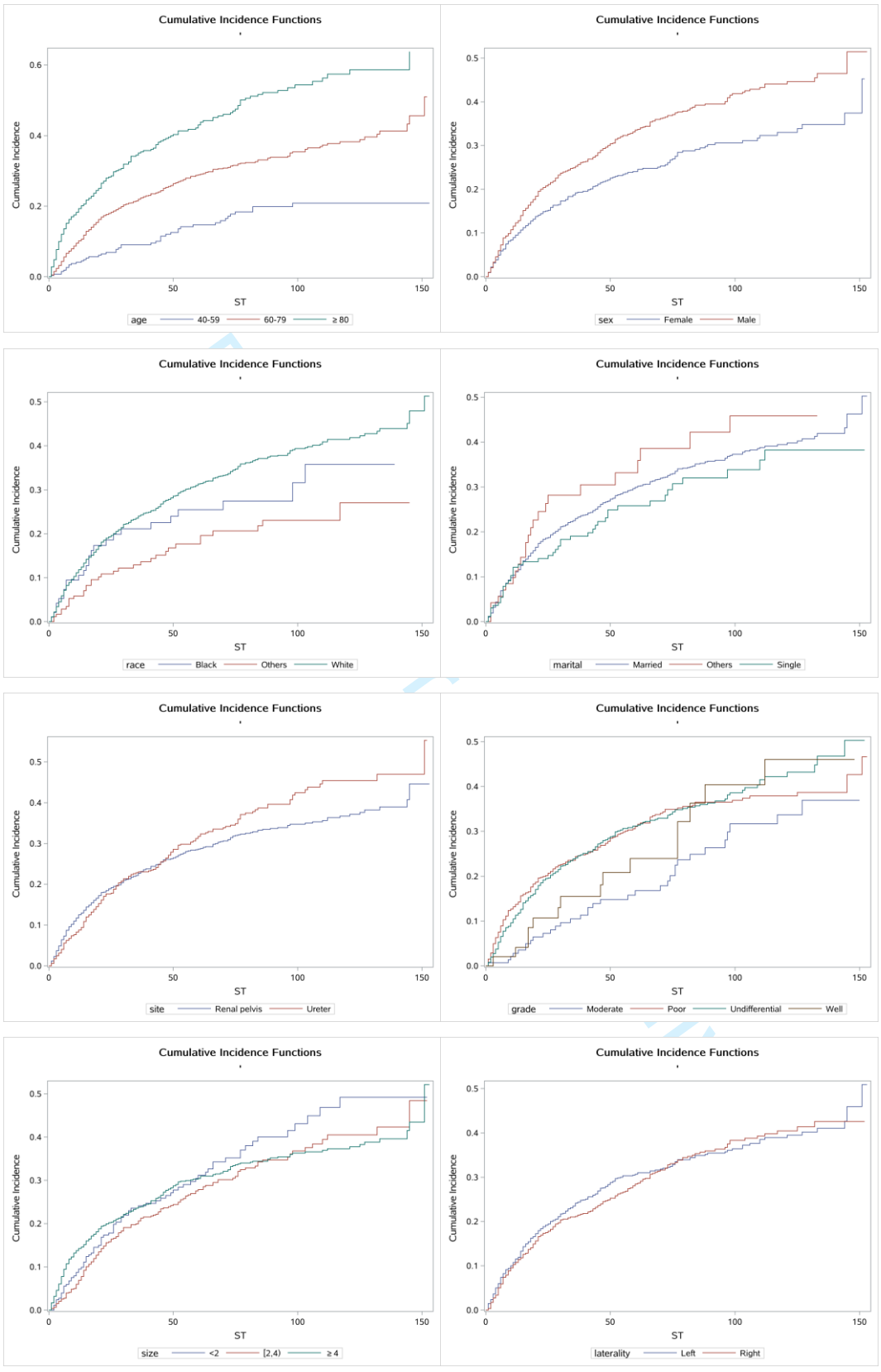


Figure 1. The CIF curves of UTUC cause-specific death. LNP: lymph nodes positive.

Figure 2


Cumulative Incidence Functions
Cumulative Incidence
ST
age 40-59 60-79 ≥ 80
Cumulative Incidence Functions
Cumulative Incidence
ST
sex Female Male
Cumulative Incidence Functions
Cumulative Incidence
ST
race Black Others White
Cumulative Incidence Functions
Cumulative Incidence
ST
marital Married Others Single
Cumulative Incidence Functions
Cumulative Incidence
ST
site Renal pelvis Ureter
Cumulative Incidence Functions
Cumulative Incidence
ST
grade Moderate Poor Undifferential Well
Cumulative Incidence Functions
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ST
size <2 [2,4) ≥ 4
Cumulative Incidence Functions
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ST
laterality Left Right

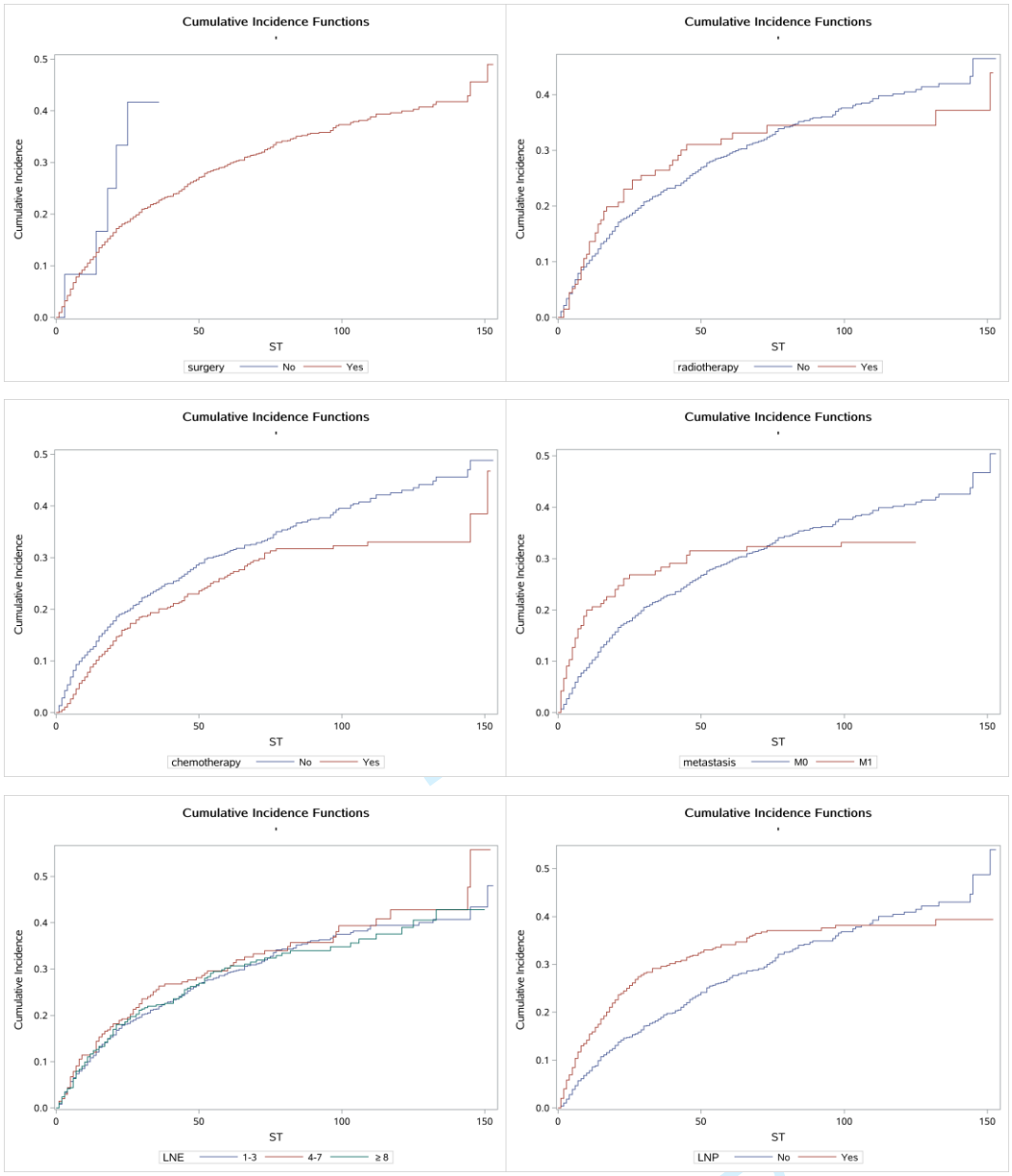

Figure 2. The CIF curves of death due to other causes of UTUC patients. LNE: lymph nodes examined; LNP: lymph nodes positive.

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A competing-risks nomogram for predicting cancer-specific death in upper-tract urothelial carcinoma: a population-based analysis

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A competing-risks nomogram for predicting cancer-specific death in upper-tract urothelial carcinoma: a population-based analysis

Running Head：Nomogram for UTUC cancer-specific death

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Abstract

Objectives: The purpose of this study was to use a competing-risks model to establish a nomogram to more accurately analyze the prognostic factors for upper-tract urothelial carcinoma (UTUC) cancer-specific death (CSD).

Setting: The program has yielded a database of all cancer patients in 18 defined geographic regions of the United States.

Participants: We selected UTUC patients from the latest edition of the Surveillance, Epidemiology, and End Results (SEER) database that covers from 1975 to 2016. After excluding patients with unknown histological grade, tumor size, and lymph node status, we finally selected 2576 patients.

Primary and secondary outcome measures: We used the Fine-Gray subdistribution proportional-hazards model for a multivariate analysis and compared the results with those obtained using cause-specific hazards model. We finally constructed a nomogram for the 3, 5, and 8 years CSD rates and tested these rates in a validation cohort.

Results: The subdistribution proportional-hazards model showed that sex, tumor size, distant metastasis, surgery status, number of lymph nodes positive (LNP), and lymph nodes ratio(LNR) were independent prognostic factors for CSD. All significant

factors associated with CSD were included in the nomogram. The 3, 5, and 8 years concordance indexes(C-indexes) were 0.714, 0.698, and 0.688 in the training cohort, respectively, and 0.693, 0.670, and 0.665 in the validation cohort.

Conclusions: The competing-risks model showed that sex, tumor size, distant metastasis, surgery status, LNP and LNR were associated with CSD. The nomogram predicts the probability of CSD in UTUC patients at 3, 5, and 8 years, which can improve the ability of clinicians to predict the survival probabilities in individual patients.

Strengths and limitations of this study:

- The study established the first competing risk nomogram for predicting the 3-, 5-, and 8-year specific mortality probability for UTUC based on a large retrospective sample, which can improve the ability of clinicians to predict the survival probabilities in individual patients.
- The established model is not comprehensive enough, because the SEER database does not include all prognostic factors for UTUC.
- The data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans.
- The model requires prospective studies to confirm its reliability.

Keywords: competing risk model, upper-tract urothelial carcinoma(UTUC), nomogram, SEER, cancer-specific death

Abbreviations: UTUC: upper-tract urothelial carcinoma; CSD: cancer-specific death; DOC: death due to other causes; SEER: Surveillance, Epidemiology, and End Results; LNE: lymph nodes examined; LNP: lymph nodes positive; K-M: Kaplan-Meier; CIF: cumulative incidence function; ICD-O-3: International Classification of Diseases for Oncology-3; LNR: lymph nodes ratio; C-index: concordance index; CS: cause-specific hazard function; SD: subdistribution proportional-hazards function

Introduction

Urothelial carcinomas are the fourth most common type of tumor,[1] and they can be located in the upper urinary tract or the lower. Upper-tract urothelial carcinoma (UTUC), which includes renal pelvis and ureter carcinoma, currently accounts for 5% of urothelial malignancies. [2] The annual incidence of UTUC is typically estimated at 1 or 2 per 100,000 inhabitants in Western countries.[3] However, the increasing morbidity and mortality associated with UTUC[4, 5] are increasing the importance of this research.

A study showed that UTUC has unique prognostic factors, which are different from bladder cancer and other urinary tract cancers.[6] Most studies analyzing the prognostic factors for UTUC have adopted the Kaplan-Meier (K-M) method or Cox regression methods.[7–9] These methods consider only a single end point when determining survival parameters. However, in addition to interest event, there are often competing events in clinical research. Competing events for cancer deaths refer to death from other causes not related to the primary cancer, such as other diseases, car collisions, and suicide. In traditional survival analysis, these events would be considered as censored, which would cause the cumulative incidence rate of cancer deaths to be overestimated. Applying standard survival analysis to competing-risks data leads to false and biased results.[10] While all-cause death as the study endpoint does not lead to competing risks bias, such an analysis could not reflect the influence of factors on the specific endpoint of cancer deaths. Therefore, the cumulative incidence function (CIF) of UTUC cancer-specific death (CSD) needs to be calculated and prognostic factors for UTUC analyzed using the Fine-Gray subdistribution proportional-hazards model.[11]

The purpose of our research was to identify the prognostic factors of UTUC based on competing risks model and used them to construct a nomogram to predict the survival rates of patients at the 3, 5, and 8 years. A nomogram is based on a prognostic model and graphically presents the predictive abilities of different prognostic factors as the lengths of line segments. This format makes it easy for

clinicians to make rapid and comprehensive judgments and to predict the probability of CSD, which has great clinical significance. Some studies have constructed competing-risks nomograms for cancers such as sarcoma and prostate cancer,[12, 13] but research related to UTUC has been lacking.

The current study was conducted to assess the effect of several factors in UTUC using a competing-risks method, and to construct a comprehensive nomogram that presents the impacts of these prognostic factors in order to guide clinical work.

Methods

Database and patients

The Surveillance, Epidemiology, and End Results (SEER) program has yielded a database of all cancer patients in 18 defined geographic regions of the United States collected by the National Cancer Institute. It is the largest cancer registry in the United States and includes information on approximately 28% of the United States population. Because part of the SEER research data is publicly available, no informed consent or institutional review board approval is required when analyzing the data. We additionally requested chemotherapy data for inclusion in our research and obtained a license for using SEER software.[14, 15]

We selected UTUC patients from the latest edition of the SEER database that covers from 1975 to 2016. The primary sites were extracted using the SEER codes of "C65.9-Renal pelvis" and "C66.9-Ureter." Patients between 2004 and 2015 were

included in the study. We included all of the histological subtypes of UTUC, according to the ICD-O-3 (third revision of the International Classification of Diseases for Oncology).The following demographic indicators were selected: age at diagnosis, sex, race, and marital status. Primary site, histological grade, tumor size, laterality, distant metastasis, surgery status, radiotherapy status, chemotherapy status, number of lymph nodes examined (LNE), lymph nodes positive (LNP), and lymph nodes ratio (LNR; calculated as the number of LNP divided by LNE) were also included as pathological characteristics. The tumor size was categorized into three groups: <2, 2–4, and ≥4 cm.[1, 16] The study outcomes included CSD and death due to other causes (DOC). The survival time was reported in the available data in months.

Exclusion criteria

Our preliminary selection of the above methods initially identified 13,581 patients. Then, in order to ensure the accuracy of the study, the exclusion criteria for the study data are as follows: unknown histological grade, unknown tumor size, and unknown lymph nodes status. The specific data selection process is shown in Figure 1. We finally chose 2576 patients for inclusion in follow-up investigations.

Figure 1

Statistical methods

We randomly divided the 2576 eligible patients into 2 groups using R software

(version 3.5.3, The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org): 70% (n=1803) in the training cohort and 30% (n=773) in the validation cohort. We first described the basic composition of each factor in the two patient cohorts using R software. The age, LNE, LNP and LNR were expressed as median and interquartile-range values, while categorical variables were represented as percentages. We evaluated differences in patient characteristics between two groups using the Student's t-test and Chi-square test.

We used the cumulative incidence function (CIF) to describe the probability of each event, and also plotted the corresponding CIF curves. And then we do univariate analysis by using Gray's test to estimate the difference in the CIF between groups. The significant variables ($P<0.05$) were put into multivariable regression model. The Fine-Gray subdistribution proportional-hazards model was used for the multivariate analysis and compared the results with using cancer-specific hazards model. Applying the standard Cox regression method ignores the presence of competing risks and hence overestimates the actual incidence of beneficial events, and so may lead to inappropriate risk stratification.[17] Several studies have confirmed that different approaches can be used in competing-risks settings for multivariate survival analysis, but subdistribution proportional-hazards model have been found to be the best predictors of survival probability.[18-20]

Finally, the results of Fine-Gray subdistribution proportional-hazards model were used to construct a nomogram of the 3, 5, and 8 years CSD rates, which was tested

using the validation cohort. We used the concordance index (C-index) and calibration plots to evaluate the differentiation ability and consistency of the established model.

All statistical tests were conducted using R software (version 3.5.3). Probability values of $P<0.05$ were considered statistically significant, and all tests were two-sided. The SEER database can be accessed free of charge, and this study was exempted from obtaining informed consent.

Patients and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Patient characteristics

The composition of each variable for the 2576 patients in the training and validation cohorts is presented in Table 1. This table indicates that the median age was 71 years in the training and validation cohorts, respectively. The majority of patients were male (60.6% and 57.4%), white (86.2% and 82.5%), and married (86.8% and 87.6%). The main UTUC sites were in the renal pelvis (63.9% and 62.7%,

respectively, in the training and validation cohorts), with the rest in the ureter. Majority of patients were in the undifferentiated stage (58.1% and 55.6%), and most of the tumors in both cohorts were larger than 4 cm. Most patients in both cohorts had received surgery, whereas a few patients had received radiotherapy or chemotherapy. Only about 9% of patients had distant metastasis.Baseline characteristics were basically similar in the training and validation cohorts.

Table 1

Univariate analysis

We calculated the 3, 5, and 8 years cumulative incidence rates of CSD and DOC. Year, laterality, and marital status were not related to either outcome (P>0.05), while age, sex, histological grade, chemotherapy status,and LNR were related to both outcomes (P<0.05). Race, primary site, tumor size, surgery status, radiotherapy status, distant metastasis, LNE, and LNP were significantly related to CSD. The corresponding CIF curves are shown in Figure 2. The cumulative incidence rates of CSD and DOC are compared in Table 2.

Figure 2, Table 2

Multivariate analysis

Our comparison of the proportional subdistribution hazards model with

cancer-specific hazards model yielded the results presented in Table 3. The cancer-specific hazards model showed that sex, tumor size, distant metastasis, LNP and LNR were prognostic factors for UTUC (P<0.001). We then constructed the Fine-Gray subdistribution proportional-hazards model, which indicated that sex (hazard ratio [HR]=1.481 for female, 95% confidence interval [CI]=1.243–1.766), tumor size (HR=1.563 for 2–4 cm, 95% CI=1.098–2.226; HR=2.204 for ≥4 cm, 95% CI=1.575–3.086), surgery status(HR=2.915 for no/unknown surgery, 95%CI=1.289-3.738), distant metastasis (HR=2.419 for distant, 95% CI=1.847-3.169), LNP(HR=1.064, 95% CI=1.022-1.107), and LNR (HR=1.871, 95% CI=1.434-2.442) were prognostic factors affecting UTUC, as presented in Table 3.

Table 3

Construction and verification of the nomogram

Figure 3 shows the nomogram we constructed according to the results of the Fine-Gray subdistribution proportional-hazards model for predicting the CSD probabilities at 3, 5, and 8 years. The figure shows that LNP had the greatest impact on the probability of CSD, followed by distant metastasis, tumor size, LNR, surgery, and sex.

We used the validation cohort to verify the nomogram after establishing it. The 3, 5, and 8 years C-indexes were 0.714, 0.698, and 0.688 for the training cohort,

respectively, and 0.693, 0.670, and 0.665 for the validation cohort. All of these values exceeded 0.6, which indicated that the model had good discrimination ability. We then tested the prediction accuracy of the model. As shown in Figure 4, the 3, 5, and 8 years calibration plots for both cohorts were very close to the standard straight line, demonstrating that the model was well calibrated.

Figures 3, 4

Discussion

The increasing incidence of UTUC[21] makes it necessary to further explore the prognostic factors for UTUC. The present study used a competing-risks model to more accurately explore the prognostic factors for UTUC, and used these factors to construct a nomogram to provide clinicians with direct guidance when they are making relevant predictions.

The application of study criteria resulted in the inclusion in 2576 patients from the SEER database, and 1542 of these patients died during the follow-up, although only 750 of the deaths were related to UTUC. This means that the number of DOC patients was almost the same as that for CSD. In this situation, if the traditional K-M or Cox survival analysis had been adopted, the DOC patients will be considered as censored. This would lead to the overestimation of the cumulative incidence rate of CSD and hence not truly reflect the prognosis.[22, 23] We overcame this shortcoming

by using competing risks model, which can properly address the situation where the available data are related to multiple potential outcomes.[24] This method was first proposed by Fine and Gray, and has also been applied in some previous studies.[17,25–26] In the presence of competing risks, there are usually two models, one is cause-specific hazards function (CS), the other is subdistribution proportional-hazards function (SD), and the latter is also called Fine-Gray model. We analyzed and compared the two models in this study. Because CS is suitable for answering etiological questions, and SD is suitable for establishing clinical prediction models and risk scores. Therefore, we used the CIF and the subdistribution proportional-hazards model to explore the impact of various factors on the prognosis of CSD.

The univariate analysis results showed that age, sex, race, primary site, histological grade, tumor size, surgery status, radiotherapy status, chemotherapy status, distant metastasis, LNE, LNP, and LNR were influencing factors for CSD, while age, sex, histological grade, chemotherapy status, and LNR were influencing factors for DOC. The cause-specific hazards model results showed that age, sex, histological grade, tumor size, distant metastasis, LNP, and LNR were prognostic factors for CSD. The subdistribution proportional-hazards model showed that sex, tumor size, surgery, distant metastasis, LNP, and LNR are independent prognostic factors for CSD.

Age is a prognostic factor for most cancers, and so is for UTUC.[27, 28] Our CS

model showed that age was a predictor of CSD, however, it is not statistically significant in the SD model. This may be because of the effect of age on DOC higher than the CSD, namely elderly patients are more likely to death of other causes, which competitively leads to the fact that the incidence of CSD does not increase significantly with age. Previous studies may have ignored competing events, and sex and race have always been controversial prognostic factors. One study showed that age and race are preoperative prognostic factors for UTUC patients.[29] In contrast, another study found no statistically significant differences in survival between males and females.[30] The competing-risks model in our study showed that sex was a risk factor for UTUC. However, since most of the patients included in the SEER database are white, the results regarding race need to be further validated.

Tumor size has always been a prognostic factor. One study found 5-year recurrence-free survival rates for patients with tumor sizes <3 cm and ≥3 cm of 46.9% and 25.8%, respectively.[31] The univariate and multivariate analyses performed in the present study indicated that tumor size was an influencing factor for CSD, with the prognosis being worse for tumors larger than 2 cm. In terms of treatment methods, surgery status was a significant prognostic factor, which was consistent with the findings of Yuval et al.[32] Thus, it should be noted that the gold standard treatment for UTUC is still surgery. However, radiotherapy status, and chemotherapy status were not influencing factors for CSD in both competing risks models. This conflicts with some previous findings,[33–35] suggesting that traditional Cox regression

analysis overestimates the effects of radiotherapy, and chemotherapy. Of course, the relative lack of information on the radiotherapy status and chemotherapy status in the SEER database may also lead to inaccurate results, and so further exploration of these indicators is needed.

Some indicators related to lymph nodes (e.g., distant lymph node metastasis, LNP, and LNE) have been found to be important clinical information for the prognosis of cancer, but whether they are independent prognostic factors for UTUC has not been determined. One study found that lymph node metastases were significantly associated with reduced disease-specific survival in univariate analysis.[36] Our research also found that distant metastasis is an important prognostic factor for CSD, in both the univariate and multivariate analyses.

It is worth noting that very few studies have investigated LNP, LNE, and LNR. Our study is the first to use the SEER database to analyze the prognostic impact of these indicators on UTUC, and the results may be more accurate than those of studies involving small samples. LNR is an emerging indicator that has been regarded as a prognostic factor in rectal cancer and breast cancer.[37, 38] Our results suggested that LNR was also an important prognostic indicators for UTUC. We found that LNE was an influencing factor for UTUC in the univariate analysis but not in the multivariate analysis. Moreover, both LNR and LNP entered the subdistribution proportional hazards model, which showed that after adjusting for the effects of LNR and LNP, LNE was no longer an independent prognostic indicator. LNP was a prognostic factor

in all of the analyses, indicating that it greatly influences the prognosis of UTUC.

We utilized the results from the above-mentioned subdistribution proportional-hazards model to construct a nomogram that graphically presents the degrees of influence of various prognostic factors. This nomogram also integrates various indicators to predict the 3, 5, and 8 years probabilities of CSD. The predictive function of nomogram has been used for different types of cancer, and has even been proposed as a new standard. For example, in order to calculate the death probability of a specific cause of death of a UTUC patient, find the patient's sex (Male or Female) on the sex row, draw a vertical line on the dot row, and get the sex score value. Repeat the above steps for tumor size, M stage, surgery, LNP and LNR. Add the point values of each variable, find the total point on the total point axis, and draw a straight downward line to get the probability of death of a UTUC patient due to a specific cause. For example, a female (30 points), with a tumor size of 1.5cm (0 points), M1 (68 points), surgery status is yes (0 points) LNP equal to 5 (15 points), and LNR equal to 0.8 (45 points), the total score is 158 points, which correspond to 3, 5, and 8 years of specific cause of death probability of 58%, 64% and 69%, respectively.

The C-indexes for the nomogram all exceeded 0.6, demonstrating that the model provides a good fit to the available data. The prediction calibration curves in Figure 4 are very close to the standard curve, which indicates that the nomogram has good predictive ability. The results for the validation cohort also show that the model is stable. This model can therefore help clinicians to quickly and easily determine the

prognosis of individual patients and provide guidance in their clinical decision-making. However, the stability of the model needs further verification.

Inevitably, our research had some limitations. First, the established model is not comprehensive enough, because the SEER database does not include all prognostic factors for UTUC. Second, the data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans. Finally, the model requires prospective studies to confirm its reliability.

5. Conclusions

In summary, this study used a competing-risks model to determine the prognostic factors for UTUC. The subdistribution proportional-hazards model showed that sex, , tumor size, surgery, distant metastasis, LNP, and LNR were associated with CSD, while LNE was not. The constructed nomogram can predict the 3, 5, and 8 years CSD probabilities of patients based on these relevant factors, which can support clinicians to make better judgments of the survival rates of individual patients.

Footnotes

Contributorship statement: JL, CZL, and SZ designed the study; QH, DDH, and FSX collected and analyzed the data; CZL and XL drafted the initial manuscript; FFZ, and XJF reviewed and edited the article; All authors read and approved the

final manuscript.

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Availability of data and materials: Ethical approval was waived, and informed consent was unnecessary because the SEER research data are anonymous and publicly available.

Patient consent for publication: Not required.

Data availability statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: The data analyses and use of the SEER database in our manuscript are in accordance with the DUA and do not require institutional review board approval or other ethics approval or consent of the study subjects.

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Table 1 The basic characteristics of the patients in this study.

Variables	Training Cohort	Validation Cohort	*p*
Number of Patients, n (%)	1803(70%)	773(30%)	
Age, Median (IQR)	71.00 (64.00, 78.00)	71.00 (63.00, 78.00)	0.710
Sex, n (%)			0.150
Female	711 (39.4)	329 (42.6)	
Male	1092 (60.6)	444 (57.4)	
Race, n (%)			0.045
Black	80 (4.4)	50 (6.5)	
Other	169 (9.4)	83 (10.7)	
White	1554 (86.2)	640 (82.8)	
Marital status, n (%)			0.656
Married	1565 (86.8)	677 (87.6)	
Others	67 (3.7)	31 (4.0)	
Single	171 (9.5)	65 (8.4)	
Year, n (%)			0.813
2004-2006	346 (19.2)	159 (20.6)	
2007-2009	439 (24.3)	181 (23.4)	
2010-2012	479 (26.6)	198 (25.6)	
2013-2015	539 (29.9)	235 (30.4)	
Site, n (%)			0.609
Renal pelvis	1152 (63.9)	485 (62.7)	
Ureter	651 (36.1)	288 (37.3)	

Grade, n (%)			0.481
Grade I	47 (2.6)	16 (2.1)	
Grade II	149 (8.3)	69 (8.9)	
Grade III	559 (31.0)	258 (33.4)	
Grade IV	1048 (58.1)	430 (55.6)	
Size, n (%)			0.188
[2,4)	559 (31.0)	268 (34.7)	
<2	262 (14.5)	106 (13.7)	
>=4	982 (54.5)	399 (51.6)	
Laterality, n (%)			0.551
Left	995 (55.2)	416 (53.8)	
Right	808 (44.8)	357 (46.2)	
Surgery, n (%)			0.203
NO/Unknown	9 (0.5)	8 (1.0)	
Yes	1794 (99.5)	765 (99.0)	
Radiotherapy, n (%)			0.931
NO/Unknown	1676 (93.0)	720 (93.1)	
Yes	127 (7.0)	53 (6.9)	
Chemotherapy, n (%)			0.938
NO/Unknown	1243 (68.9)	531 (68.7)	
Yes	560 (31.1)	242 (31.3)	
Distant metastasis, n (%)			0.053
M0	1652 (91.6)	689 (89.1)	

M1	151 (8.4)	84 (10.9)	
LNE, Median (IQR)	3.00 (1.00, 7.00)	3.00 (1.00, 7.00)	0.627
LNP, Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.542
LNR, Median (IQR)	0.00 (0.00, 0.50)	0.00 (0.00, 0.33)	0.546

Abbreviations: IQR, interquartile-range; COD, cause of death; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Table 2 The cumulative incidences of CSD and DOC among patients with UTUC.

Variables	Cause-specific death (%)				Death due to other causes (%)			
	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	P	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	P
Age				<0.001				<0.001
Sex				<0.001				<0.001
Male	22.903 (22.843-22.964)	27.131 (27.064-27.197)	29.457 (29.386-29.528)		25.697 (25.634-25.760)	33.645 (33.573-33.717)	40.755 (40.673-40.837)	
Female	33.320 (33.236-33.405)	38.157 (38.066-38.247)	40.339 (40.245-40.434)		18.710 (18.639-18.780)	24.144 (24.063-24.225)	29.031 (28.937-29.125)	
Race				0.008				0.057
White	25.881 (25.828-25.934)	29.921 (29.864-29.979)	31.856 (31.796-31.916)		23.502 (23.451-23.554)	30.839 (30.780-30.898)	37.596 (37.528-37.664)	
Black	35.688 (35.423-35.952)	44.479 (44.194-44.763)	48.470 (48.178-48.762)		22.782 (22.555-23.009)	27.889 (27.638-28.139)	30.253 (29.987-30.519)	
Other	33.577 (33.399-33.755)	39.945 (39.752-40.138)	43.895 (43.688-44.102)		17.728 (17.586-17.869)	22.120 (21.960-22.281)	25.822 (25.642-26.003)	
Marital status				0.589				0.861
Married	26.658 (26.605-26.711)	31.026 (30.968-31.083)	33.392 (33.330-33.453)		23.164 (23.113-23.215)	30.058 (30.000-30.117)	36.522 (36.455-36.589)	
Single	28.974 (28.808-29.140)	35.046 (34.863-35.229)	37.001 (36.813-37.189)		20.973 (20.824-21.122)	28.316 (28.143-28.489)	32.867 (32.676-33.058)	

Others	30.406 (30.132-30.681)	32.762 (32.475-33.048)	32.762 (32.475-33.048)		22.481 (22.231-22.730)	30.490 (30.186-30.794)	35.083 (34.731-35.436)	
Year				0.426				0.523
2004-2006	27.535 (27.424-27.646)	31.905 (31.789-32.021)	33.656 (33.538-33.773)		24.057 (23.951-24.164)	32.211 (32.095-32.327)	38.629 (38.508-38.750)	
2007-2009	29.665 (29.564-29.765)	34.035 (33.930-34.139)	36.463 (36.356-36.569)		22.606 (22.513-22.698)	28.351 (28.252-28.451)	34.151 (34.045-34.256)	
2010-2012	26.033 (25.940-26.126)	30.269 (30.170-30.368)	—		21.838 (21.751-21.926)	28.813 (28.715-28.910)	—	
2013-2015	25.678 (25.572-25.784)	29.114 (28.976-29.252)	29.114 (28.976-29.252)		23.766 (23.661-23.871)	27.273 (27.135-27.411)	27.273 (27.135-27.411)	
Site				<0.001				0.161
Renal pelvis	30.986 (30.921-31.051)	36.259 (36.189-36.329)	38.503 (38.430-38.577)		22.942 (22.883-23.001)	28.605 (28.539-28.672)	33.500 (33.425-33.576)	
Ureter	19.946 (19.870-20.021)	23.033 (22.951-23.114)	25.368 (25.279-25.456)		22.948 (22.868-23.028)	32.131 (32.037-32.225)	40.713 (40.604-40.822)	
Grade				<0.001				0.043
Well	13.707 (13.463-13.950)	13.707 (13.463-13.950)	13.707 (13.463-13.950)		18.635 (18.356-18.914)	21.710 (21.406-22.015)	40.163 (39.717-40.609)	
Moderate	10.664 (10.543-10.785)	13.393 (13.255-13.530)	15.852 (15.696-16.008)		10.147 (10.028-10.267)	18.691 (18.530-18.853)	27.546 (27.340-27.752)	
Poor	30.407 (30.315-30.498)	35.156 (35.059-35.253)	37.336 (37.236-37.437)		24.420 (24.335-24.506)	30.727 (30.633-30.822)	36.164 (36.060-36.269)	
Undifferential	28.133 (28.066-28.200)	33.013 (32.939-33.086)	35.492 (35.413-35.572)		24.207 (24.142-24.271)	31.584 (31.510-31.658)	37.338 (37.252-37.424)	

Size				<0.001			0.727
<2	11.702 (11.603-11.801)	15.012 (14.896-15.129)	18.912 (18.770-19.054)	23.698 (23.568-23.828)	30.965 (30.815-31.114)	41.203 (41.019-41.386)	
[2,4)	20.339 (20.257-20.421)	25.968 (25.875-26.061)	27.430 (27.333-27.527)	21.685 (21.601-21.769)	29.688 (29.589-29.787)	38.966 (38.846-39.085)	
≥4	34.800 (34.728-34.872)	38.856 (38.781-38.932)	41.137 (41.058-41.216)	23.457 (23.393-23.521)	29.756 (29.684-29.828)	33.400 (33.322-33.479)	
Laterality				0.944			0.393
Left	26.970 (26.903-27.037)	31.835 (31.762-31.908)	33.636 (33.560-33.713)	22.586 (22.523-22.650)	29.551 (29.479-29.624)	35.006 (34.923-35.089)	
Right	27.092 (27.017-27.167)	31.010 (30.929-31.091)	33.867 (33.781-33.954)	23.335 (23.264-23.406)	30.305 (30.223-30.387)	37.564 (37.469-37.659)	
Surgery				0.001			0.980
Yes	26.715 (26.665-26.765)	31.206 (31.152-31.260)	33.490 (33.432-33.547)	22.940 (22.893-22.988)	29.950 (29.895-30.004)	36.234 (36.171-36.296)	
NO/Unknown	77.778 (76.910-78.646)	—	—	22.222 (21.522-22.923)	—	—	
Radiotherapy				<0.001			0.998
Yes	44.203 (43.994-44.413)	50.656 (50.438-50.873)	52.100 (51.879-52.321)	25.971 (25.788-26.155)	32.137 (31.936-32.339)	34.905 (34.692-35.117)	
NO/Unknown	25.670 (25.619-25.721)	29.946 (29.891-30.001)	32.280 (32.221-32.339)	22.699 (22.650-22.748)	29.723 (29.667-29.779)	36.255 (36.190-36.320)	
Chemotherapy				<0.001			0.003

Yes	36.276 (36.177-36.375)	41.780 (41.674-41.885)	43.328 (43.220-43.436)		20.156 (20.074-20.239)	26.842 (26.746-26.938)	30.774 (30.670-30.879)	
NO/Unknown	22.979 (22.922-23.035)	27.025 (26.964-27.087)	29.597 (29.530-29.664)		24.177 (24.119-24.235)	31.265 (31.200-31.331)	38.492 (38.416-38.569)	
Distant metastasis				<0.001				0.641
No	23.438 (23.388-23.488)	28.067 (28.012-28.122)	30.550 (30.491-30.609)		22.674 (22.624-22.723)	29.966 (29.909-30.024)	36.800 (36.734-36.866)	
Yes	65.586 (65.407-65.765)	67.967 (67.789-68.144)	67.967 (67.789-68.144)		25.548 (25.384-25.713)	28.750 (28.577-28.922)	28.750 (28.577-28.922)	
LNE	—	—	—	<0.001	—	—	—	0.941
LNP	—	—	—	<0.001	—	—	—	0.448
LNR	—	—	—	<0.001	—	—	—	<0.001

Abbreviations: CI, confidence interval; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Table 3 Selected variables by proportional subdistribution hazard model and multivariate cause-specific hazards model.

Variables	Proportional subdistribution hazards model				Cause-specific hazards model			
	Coefficient	sdHR	95%CI	*P*	Coefficient	csHR	95%CI	*P*
Age	-0.004	0.996	0.987-1.005	0.339	0.009	1.009	1.000-1.018	0.043
Sex								
Male	Reference				Reference			
Female	0.393	1.481	1.243-1.766	<.0001	0.307	1.360	1.141-1.620	0.001
Race								
White	Reference				Reference			
Black	0.240	1.272	0.872-1.856	0.212	0.347	1.414	0.988-2.024	0.058
Other	0.200	1.222	0.930-1.606	0.151	0.164	1.178	0.899-1.544	0.235
Site								
Renal pelvis	Reference				Reference			
Ureter	-0.106	0.900	0.737-1.097	0.296	-0.096	0.909	0.740-1.117	0.362
Grade								
Well	Reference				Reference			
Moderate	-0.034	0.966	0.398-2.344	0.939	0.009	1.009	0.407-2.501	0.985
Poor	0.763	2.144	0.970-4.738	0.059	0.902	2.463	1.091-5.563	0.030
Undifferential	0.658	1.932	0.878-4.249	0.102	0.773	2.167	0.963-4.878	0.062
Size								
<2	Reference				Reference			
[2,4)	0.447	1.563	1.098-2.226	0.013	0.425	1.529	1.054-2.219	0.025

≥4	0.790	2.204	1.575-3.086	<.0001	0.878	2.407	1.686-3.436	<.0001
Surgery								
Yes	Reference				Reference			
NO/Unknown	0.786	2.195	1.289-3.738	0.004	0.741	2.098	0.979-4.492	0.057
Radiotherapy								
Yes	Reference				Reference			
NO/Unknown	-0.229	0.795	0.588-1.075	0.136	-0.261	0.771	0.583-1.019	0.067
Chemotherapy								
Yes	Reference				Reference			
NO/Unknown	0.021	1.021	0.826-1.263	0.848	0.157	1.170	0.959-1.428	0.122
Distant metastasis								
No	Reference				Reference			
Yes	0.883	2.419	1.847-3.169	<.0001	1.255	3.509	2.751-4.476	<.0001
LNE	-0.012	0.988	0.970-1.006	0.196	-0.013	0.987	0.972-1.002	0.090
LNP	0.062	1.064	1.022-1.107	0.002	0.068	1.070	1.030-1.111	0.000
LNR	0.627	1.871	1.434-2.442	<.0001	0.925	2.522	1.947-3.266	<.0001

Abbreviations: sdHR, subdistribution hazard ratio; csHR, Cause-specific hazard ratio; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Figure legends

Figure 1. Data selection flowchart.

Figure 2. The CIF curves of UTUC cancer-specific death (CSD). Race, primary site, tumor size, surgery status, radiotherapy status, distant metastasis, LNE, and LNP were significantly related to the patients of CSD. LNE: lymph nodes examined; LNP: lymph nodes positive.

Figure 3. Nomogram based on the competing risk analysis to predict cancer-specific death probabilities at 3, 5, and 8 years for UTUC patients. LNE: lymph nodes examined; LNP: lymph nodes positive.

Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years calibration plots of the training (A, B, C) and validation (D, E, F) cohort.

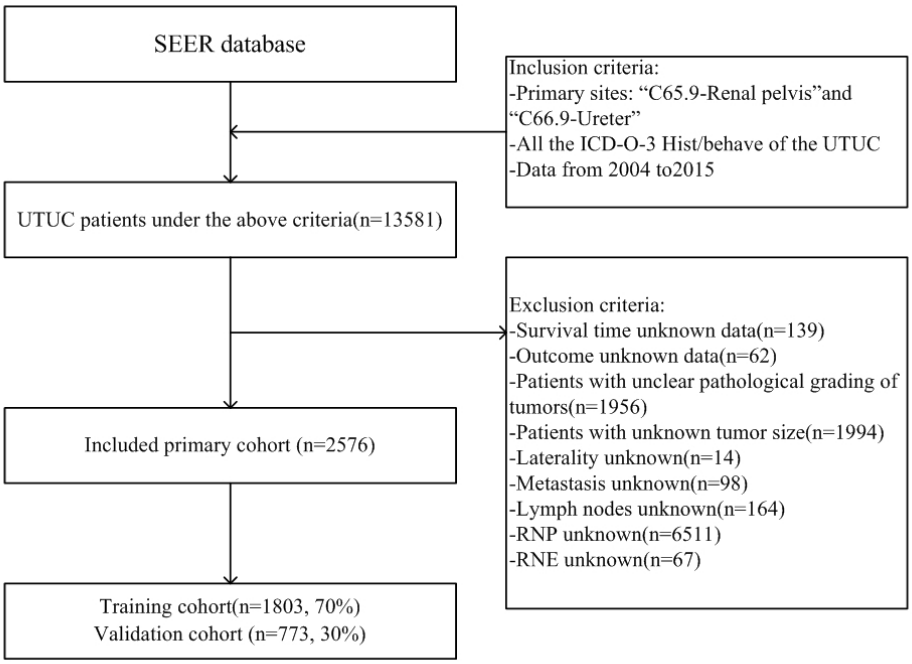

Figure 1. Data selection flowchart.

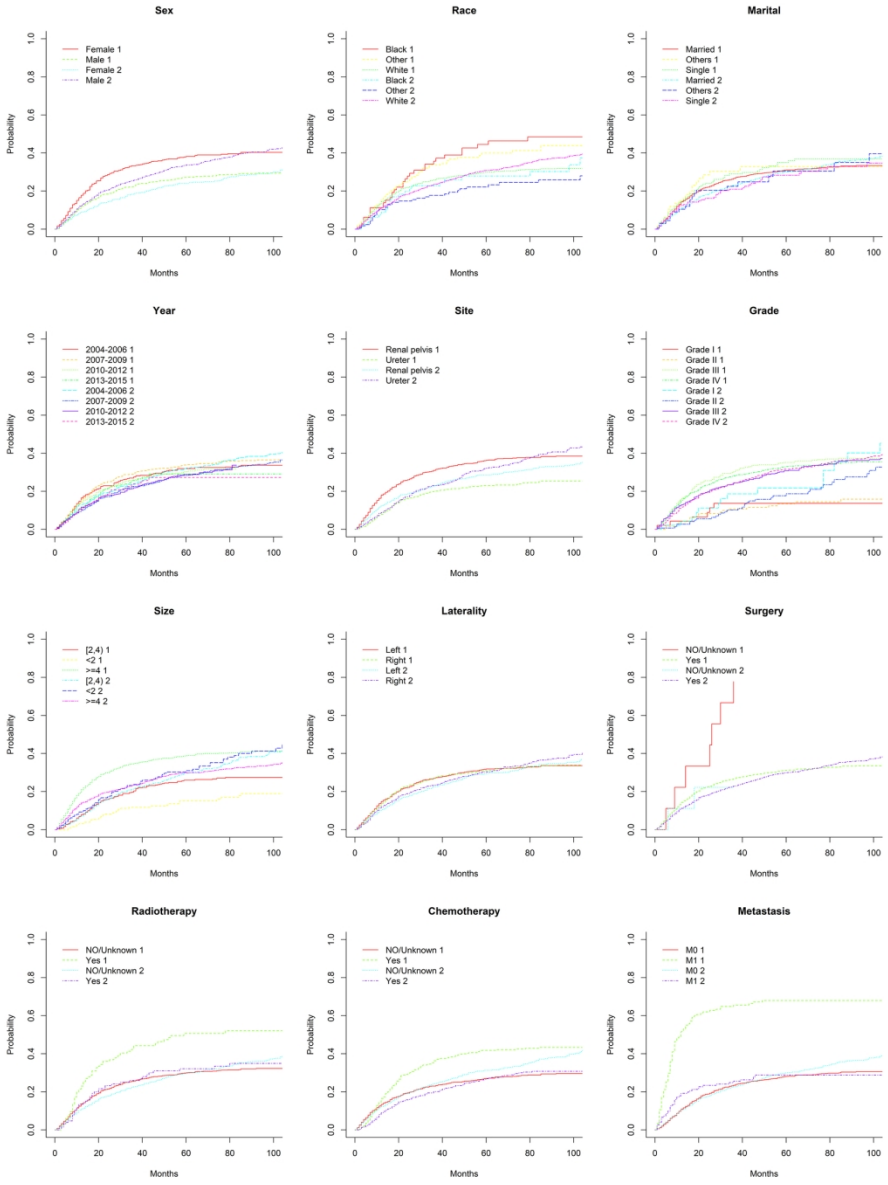

Figure 2. The CIF curves of UTUC cancer-specific death (CSD). Race, primary site, tumor size, surgery status, radiotherapy status, distant metastasis, LNE, and LNP were significantly related to the patients of CSD. LNE: lymph nodes examined; LNP: lymph nodes positive.

149x199mm (300 x 300 DPI)

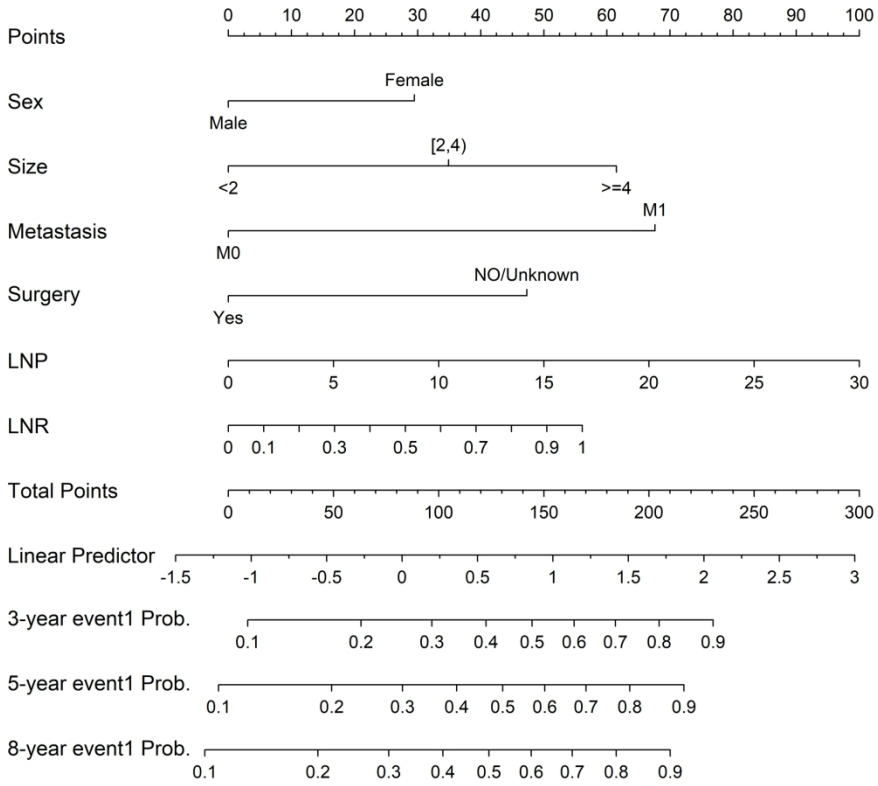

Figure 3. Nomogram based on the competing risk analysis to predict cancer-specific death probabilities at 3, 5, and 8 years for UTUC patients. LNE: lymph nodes examined; LNP: lymph nodes positive.

203x203mm (300 x 300 DPI)

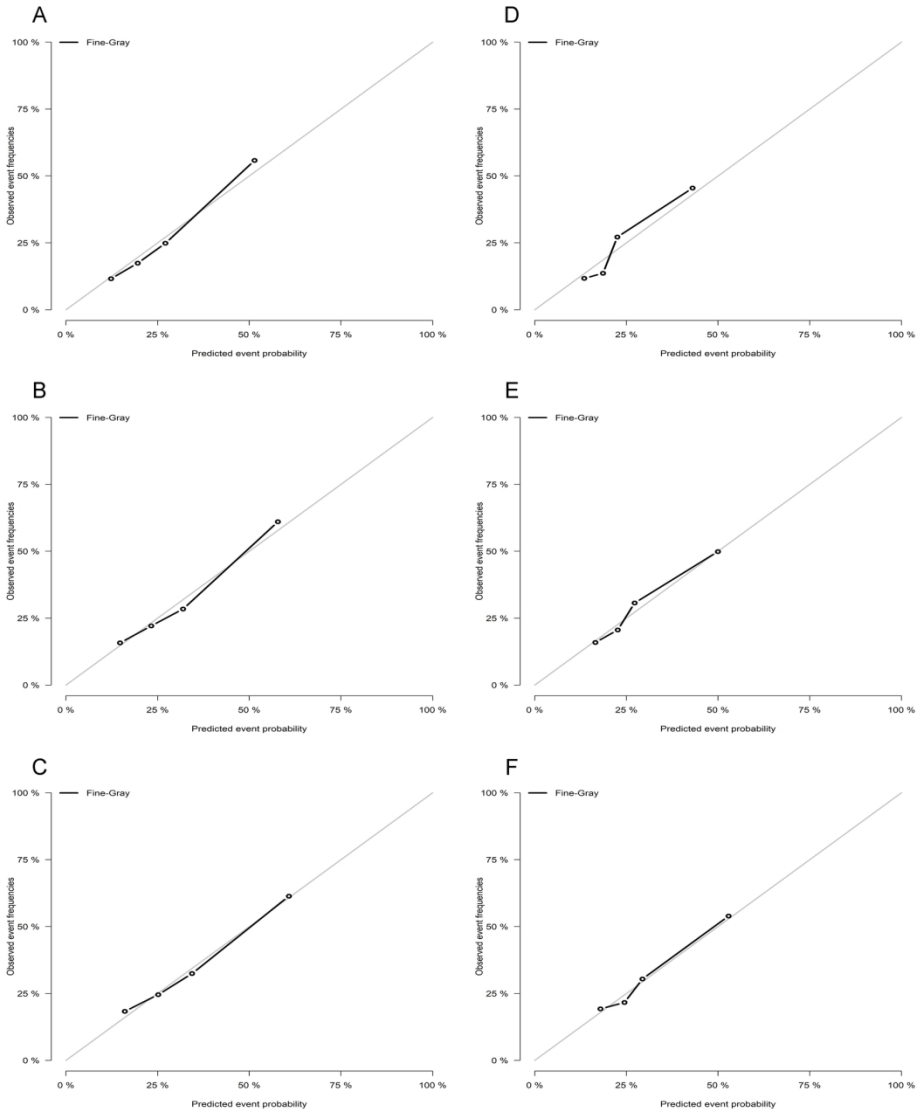

Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years calibration plots of the training (A, B, C) and validation (D, E, F) cohort.

160x186mm (300 x 300 DPI)

TRIPOD Checklist: Prediction Model Development

Section	Item	Checklist description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract				
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.		
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.		
Introduction				
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.		
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.		
Methods				
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, ifapplicable.		
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.		
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.		
	5b	Describe eligibility criteria for participants.		
	5c	Give details of treatments received, if relevant.		
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.		
	6b	Report any actions to blind assessment of the outcome to be predicted.		
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.		
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.		
Sample size	8	Explain how the study size was arrived at.		

Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.		
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.		
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.		
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.		
Risk groups	11	Provide details on how risk groups were created, if done.		
Results				
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.		
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.		
Model development	14a	Specify the number of participants and outcome events in each analysis.		
	14b	If done, report the unadjusted association between each candidate predictor and outcome.		
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).		
	15b	Explain how to the use the prediction model.		
Model performance	16	Report performance measures (with CIs) for the prediction model.		
Discussion				
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).		
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.		
Implications	20	Discuss the potential clinical use of the model and implications for future research.		
Other information				
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.		
Funding	22	Give the source of funding and the role of the funders for the present study.		

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A competing-risks nomogram for predicting cancer-specific death in upper-tract urothelial carcinoma: a population-based analysis

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A competing-risks nomogram for predicting cancer-specific death in upper-tract urothelial carcinoma: a population-based analysis

Running Head：Nomogram for UTUC cancer-specific death

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Abstract

Objectives: The purpose of this study was to use a competing-risks model to establish a nomogram to more accurately analyze the prognostic factors for upper-tract urothelial carcinoma (UTUC) cancer-specific death (CSD).

Design: Retrospective observational cohort study.

Setting: The program has yielded a database of all cancer patients in 18 defined geographic regions of the United States.

Participants: We selected UTUC patients from the latest edition of the Surveillance, Epidemiology, and End Results (SEER) database that covers from 1975 to 2016. After excluding patients with unknown histological grade, tumor size, and lymph node status, we finally selected 2576 patients.

Primary and secondary outcome measures: We used the Fine-Gray proportional subdistribution hazards model for a multivariate analysis and compared the results with those obtained using cause-specific hazards model. We finally constructed a nomogram for the 3, 5, and 8 years CSD rates and tested these rates in a validation cohort.

Results: The proportional subdistribution hazards model showed that sex, tumor size, distant metastasis, surgery status, number of lymph nodes positive (LNP), and lymph nodes ratio(LNR) were independent prognostic factors for CSD. All significant factors associated with CSD were included in the nomogram. The 3, 5, and 8 years concordance indexes were 0.719, 0.702, and 0.692 in the training cohort, and 0.701, 0.675, and 0.668 in the validation cohort, respectively.

Conclusions: The competing-risks model showed that sex, tumor size, distant metastasis, surgery status, LNP and LNR were associated with CSD. The nomogram predicts the probability of CSD in UTUC patients at 3, 5, and 8 years, which can improve the ability of clinicians to predict the survival probabilities in individual patients.

Strengths and limitations of this study:

- The study established the first competing risk nomogram for predicting the 3-, 5-, and 8-year specific mortality probability for UTUC based on a large retrospective sample, which can improve the ability of clinicians to predict the survival probabilities in individual patients.
- The established model is not comprehensive enough, because the SEER database does not include all prognostic factors for UTUC.
- The data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans.
- The model requires prospective studies to confirm its reliability.

Keywords: competing risk model, upper-tract urothelial carcinoma(UTUC), nomogram, SEER, cancer-specific death

Abbreviations: UTUC: upper-tract urothelial carcinoma; CSD: cancer-specific death; DOC: death due to other causes; SEER: Surveillance, Epidemiology, and End Results; LNE: lymph nodes examined; LNP: lymph nodes positive; K-M: Kaplan-Meier; CIF: cumulative incidence function; ICD-O-3: International Classification of Diseases for Oncology-3; LNR: lymph nodes ratio; C-index:

concordance index; CS: cause-specific hazards model; SD: proportional subdistribution hazards model

Introduction

Urothelial carcinomas are the fourth most common type of tumor,[1] and they can be located in the upper urinary tract or the lower. Upper-tract urothelial carcinoma (UTUC), which includes renal pelvis and ureter carcinoma, currently accounts for 5% of urothelial malignancies. [2] The annual incidence of UTUC is typically estimated at 1 or 2 per 100,000 inhabitants in Western countries.[3] However, the increasing morbidity and mortality associated with UTUC[4, 5] are increasing the importance of this research.

A study showed that UTUC has unique prognostic factors, which are different from bladder cancer and other urinary tract cancers.[6] Most studies analyzing the prognostic factors for UTUC have adopted the Kaplan-Meier (K-M) method or Cox regression methods.[7–9] These methods only consider a single endpoint when determining survival parameters. However, in clinical research, in addition to events of interest, there are often competing events. Competing events for cancer deaths refer to death from other causes not related to the primary cancer, such as other diseases, car collisions, and suicide. In traditional survival analysis, these events will be considered as censored, which will make the cumulative incidence of cancer deaths overestimated. Applying standard survival analysis to competing-risks data leads to false and biased results.[10] Although the use of all-cause death as the study endpoint does not cause a competing risks bias, such an analysis cannot reflect the influence of

factors on the specific endpoint of cancer death. Therefore, the cumulative incidence function (CIF) of UTUC cancer-specific death (CSD) needs to be calculated and prognostic factors for UTUC analyzed using the Fine-Gray proportional subdistribution hazards model.[11]

A nomogram is based on a prognostic model and graphically presents the predictive abilities of different prognostic factors as the lengths of line segments. This format makes it easy for clinicians to make rapid and comprehensive judgments and to predict the probability of CSD, which has great clinical significance. Some studies have constructed competing-risks nomograms for cancers such as sarcoma and prostate cancer,[12, 13] but research related to UTUC has been lacking.

The purpose of our research was to identify the prognostic factors of UTUC based on competing risks model and used them to construct a nomogram to predict the survival rates of patients at the 3, 5, and 8 years.

Methods

Database and patients

The Surveillance, Epidemiology, and End Results (SEER) program has yielded a database of all cancer patients in 18 defined geographic regions of the United States collected by the National Cancer Institute. It is the largest cancer registry in the United States and includes information on approximately 28% of the United States population. Because part of the SEER research data is publicly available, no informed consent or institutional review board approval is required when analyzing the data.

We additionally requested chemotherapy data for inclusion in our research and obtained a license for using SEER software.[14, 15]

We selected UTUC patients from the latest edition of the SEER database that covers from 1975 to 2016. The primary sites were extracted using the SEER codes of "C65.9-Renal pelvis" and "C66.9-Ureter." Patients between 2004 and 2015 were included in the study. We included all of the histological subtypes of UTUC, according to the ICD-O-3 (third revision of the International Classification of Diseases for Oncology).The following demographic indicators were selected: age at diagnosis, sex, race, and marital status. Primary site, histological grade, tumor size, laterality, distant metastasis, surgery status, radiotherapy status, chemotherapy status, number of lymph nodes examined (LNE), lymph nodes positive (LNP), and lymph nodes ratio (LNR; calculated as the number of LNP divided by LNE) were also included as pathological characteristics. The tumor size was categorized into three groups: <2, 2–4, and ≥4 cm.[1, 16] The study outcomes included CSD and death due to other causes (DOC). The survival time was reported in the available data in months.

Exclusion criteria

Our preliminary selection of the above methods initially identified 13,581 patients. Then, in order to ensure the accuracy of the study, the exclusion criteria for the study data are as follows: unknown histological grade, unknown tumor size, and unknown lymph nodes status. The specific data selection process is shown in Figure 1. We finally chose 2576 patients for inclusion in follow-up investigations.

Figure 1

Statistical methods

We randomly divided the 2576 eligible patients into 2 groups using R software (version 3.5.3, The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org): 70% (n=1803) in the training cohort and 30% (n=773) in the validation cohort. We first described the basic composition of each factor in the two patient cohorts using R software. The age, LNE, LNP and LNR were expressed as median and interquartile-range values, while categorical variables were represented as percentages. We evaluated differences in patient characteristics between two groups using the Student's t-test and Chi-square test.

We used the cumulative incidence function (CIF) to describe the probability of each event, and also plotted the corresponding CIF curves. And the Gray's test was used for univariate analysis to estimate the difference in CIF between groups. Significant variables ($P<0.05$) were included in the multivariate regression model. The Fine-Gray proportional subdistribution hazards model was used for the multivariate analysis and compared with the results of cause-specific hazards model. Applying the standard Cox regression method ignores the presence of competing risks and hence overestimates the actual incidence of beneficial events, and so may lead to inappropriate risk stratification.[17] Several studies have confirmed that different approaches can be used in competing-risks settings for multivariate survival analysis, but proportional subdistribution hazards model have been found to be the best method to predict the survival probability.[18-20]

Finally, the results of Fine-Gray proportional subdistribution hazards model were used to construct a nomogram of the 3, 5, and 8 years CSD rates. We used the concordance index (C-index) and calibration plots to evaluate the differentiation ability and consistency of the established model in both training and validation cohorts.

All statistical tests were conducted using R software (version 3.5.3). Probability values of $P<0.05$ were considered statistically significant, and all tests were two-sided. The SEER database can be accessed free of charge, and this study was exempted from obtaining informed consent.

Patients and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Patient characteristics

The composition of each variable for the 2576 patients in the training and validation cohorts is presented in Table 1. This table indicates that the median age was 71 years in the training and validation cohorts, respectively. The majority of patients were male (60.6% and 57.4%), white (86.2% and 82.5%), and married (86.8% and 87.6%). The main UTUC sites were in the renal pelvis (63.9% and 62.7%, respectively, in the training and validation cohorts), with the rest in the ureter.

Majority of patients were in the undifferentiated stage (58.1% and 55.6%), and most of the tumors in both cohorts were larger than 4 cm. Most patients in both cohorts had received surgery, whereas a few patients had received radiotherapy or chemotherapy. Only about 9% of patients had distant metastasis. The baseline characteristics of the training cohorts and validation cohorts were basically similar.

Table 1

Univariate analysis

We calculated the 3, 5, and 8 years cumulative incidence rates of CSD and DOC. Year, laterality, and marital status were not related to either outcome (P>0.05), while age, sex, histological grade, chemotherapy status, and LNR were related to both outcomes (P<0.05). Race, primary site, tumor size, surgery status, radiotherapy status, distant metastasis, LNE, and LNP were significantly related to CSD. The corresponding CIF curves are shown in Figure 2. The cumulative incidence of CSD and DOC are compared in Table 2.

Figure 2, Table 2

Multivariate analysis

Our comparison of the proportional subdistribution hazards model with cancer-specific hazards model yielded the results presented in Table 3. The cancer-specific hazards model showed that sex, tumor size, distant metastasis, LNP and LNR were prognostic factors for UTUC (P<0.001). We then constructed the Fine-Gray proportional subdistribution hazards model, which indicated that sex

(hazard ratio [HR]=1.480 for female, 95% confidence interval [CI]=1.241–1.764), tumor size (HR=1.556 for 2–4 cm, 95% CI=1.092–2.216; HR=2.205 for ≥4 cm, 95% CI=1.575–3.087), surgery status(HR=2.205 for no/unknown surgery, 95%CI=1.292-3.761), distant metastasis (HR=2.414 for distant, 95% CI=1.842-3.163), LNP(HR=1.064, 95% CI=1.022-1.107), and LNR (HR=1.873, 95% CI=1.435-2.445) were prognostic factors affecting UTUC, as presented in Table 3.

Table 3

Construction and verification of the nomogram

Figure 3 shows the nomogram we constructed according to the results of the Fine-Gray proportional subdistribution hazards model for predicting the CSD probabilities at 3, 5, and 8 years. The figure shows that LNP had the greatest impact on the probability of CSD, followed by distant metastasis, tumor size, LNR, surgery, and sex.

We used both the training and validation cohorts to verify the nomogram after establishing it. The 3, 5, and 8 years C-indexes were 0.719, 0.702, and 0.692 for the training cohort, respectively, and 0.701, 0.675, and 0.668 for the validation cohort. All of these values exceeded 0.6, which indicated that the model had good discrimination ability. We then tested the prediction accuracy of the model. As shown in Figure 4, the 3, 5, and 8 years calibration plots for both cohorts were very close to the standard straight line, demonstrating that the model was well calibrated.

Figures 3, 4

Discussion

The increasing incidence of UTUC[21] makes it necessary to further explore the prognostic factors for UTUC. The present study used a competing-risks model to more accurately explore the prognostic factors for UTUC, and used these factors to construct a nomogram to provide clinicians with direct guidance when they are making relevant predictions.

The application of study criteria resulted in the inclusion in 2576 patients from the SEER database, and 1542 of these patients died during the follow-up, although only 750 of the deaths were related to UTUC. This meant that the number of DOC patients was almost the same as that for CSD. In this situation, if the traditional K-M or Cox survival analysis had been adopted, the DOC patients will be regarded as censored. This will lead to an overestimation of the cumulative incidence of CSD, which cannot truly reflect the prognosis.[22, 23] We overcame this shortcoming by using competing risks model, which can properly address the situation where the available data are related to multiple potential outcomes.[24] This method was first proposed by Fine and Gray, and has also been applied in some previous studies.[17,25–26] In the case of competing risks, there are usually two models. One is cause-specific hazards model (CS), the other is the proportional subdistribution hazards model (SD), which is also known as the Fine-Gary model. In present study, the two models were analyzed and compared. Because CS is suitable for answering etiological questions, and SD is suitable for establishing clinical prediction models and risk scores. Therefore, we used the CIF and the proportional subdistribution

hazards model to explore the impact of various factors on the prognosis of CSD.

The univariate analysis results showed that age, sex, race, primary site, histological grade, tumor size, surgery status, radiotherapy status, chemotherapy status, distant metastasis, LNE, LNP, and LNR were influencing factors for CSD, while age, sex, histological grade, chemotherapy status, and LNR were influencing factors for DOC. The cause-specific hazards model results showed that age, sex, histological grade, tumor size, distant metastasis, LNP, and LNR were prognostic factors for CSD. The proportional subdistribution hazards model showed that sex, tumor size, surgery, distant metastasis, LNP, and LNR are independent prognostic factors for CSD.

Age is generally considered to be a prognostic factor for most cancers, and so is for UTUC.[27, 28] Our CS model showed that age was a predictor of CSD, however, it was not statistically significant in the SD model. This may be because of the effect of age on DOC is higher than the CSD, namely elderly patients are more likely to death of other causes, which competitively leads to the fact that the incidence of CSD does not increase significantly with age. Sex and race have always been controversial prognostic factors. One study showed that race was a preoperative prognostic factors for UTUC patients.[29] And another study found no statistically significant differences in survival between males and females.[30] However, the competing-risks model in our study showed that sex was a risk factor for UTUC, while race was not. This may be because previous studies ignored the effect of competing risks. However, since most of the patients included in the SEER database are white, the results

regarding race need to be further validated.

Tumor size is also generally considered to be related to cancer prognosis. One study found 5-year recurrence-free survival rates for UTUC patients with tumor sizes <3 cm and ≥3 cm of 46.9% and 25.8%, respectively.[31] The univariate and multivariate analyses performed in the present study also indicated that tumor size was an influencing factor for CSD, with the prognosis being worse for tumors larger than 2 cm. In addition, our research also found that distant metastasis was an important risk factor for CSD. In terms of treatment methods, our study suggested that surgery status was a significant prognostic factor, which was consistent with the findings of Yuval et al.[32] In fact, surgery has long been considered the gold standard of UTUC treatment. However, radiotherapy status, and chemotherapy status were not influencing factors for CSD in both competing risks models. This conflicted with some previous findings,[33–35] suggesting that traditional Cox regression analysis overestimated the effects of radiotherapy and chemotherapy. Of course, the relative lack of information on the radiotherapy status and chemotherapy status in the SEER database may also lead to inaccurate results, and so further exploration of these indicators is needed.

Some indicators related to lymph nodes (e.g., distant lymph node metastasis, LNP, and LNE) have been found to be important clinical information for the prognosis of cancer, but whether they are independent prognostic factors for UTUC has not been determined. One study found that lymph node metastases were significantly associated with reduced cancer-specific survival in univariate

analysis.[36] It is worth noting that very few studies have investigated LNP, LNE, and LNR. Our study is the first to use the SEER database to analyze the prognostic impact of these indicators on UTUC, and the results may be more accurate than those of studies involving small samples. LNR is an emerging indicator that has been regarded as a prognostic factor in rectal cancer and breast cancer.[37, 38] Our results also suggested that LNR was an important prognostic factor of UTUC. We found that LNE was an influencing factor for UTUC in the univariate analysis but not in the multivariate analysis. Moreover, both LNR and LNP entered the proportional subdistribution hazards model, which showed that after adjusting for the effects of LNR and LNP, LNE was no longer an independent prognostic indicator. LNP was a prognostic factor in all of the analyses, indicating that it greatly influences the prognosis of UTUC.

We utilized the results from the above-mentioned proportional subdistribution hazards model to construct a nomogram that graphically presents the degrees of influence of various prognostic factors. This nomogram can be used to predict the 3, 5, and 8 years probabilities of CSD in UTUC patients. The predictive function of nomogram has been used for different types of cancer, and has even been proposed as a new standard. The nomogram is easy to use. In order to calculate the CSD probability of a UTUC patient, find the patient's sex (Male or Female) on the sex row, draw a vertical line on the dot row, and get the sex score value. Repeat the above steps for tumor size, M stage, surgery, LNP and LNR. Add the score values of each variable, find the total point on the total point axis, and draw a straight downward line

to get the 3, 5 and 8 years CSD probability of the UTUC patient. For example, a female (30 points), with a tumor size of 1.5cm (0 points), at M1 stage(68 points), had surgery performed (0 points), LNP equal to 5 (15 points), and LNR equal to 0.8 (45 points), the total score is 158 points, which corresponds to 3, 5, and 8 years CSD probability of 58%, 64% and 69%, respectively.

The C-indexes for the nomogram all exceeded 0.6, demonstrating that the model provided a good fit to the available data. The prediction calibration curves in Figure 4 were very close to the standard curve, which indicated that the nomogram had good predictive ability. The results for the validation cohort also showed that the model was stable. This model can therefore help clinicians to quickly and easily determine the prognosis of individual patients and provide guidance in their clinical decision-making. However, the stability of the model needs further verification.

Our study used the large sample size and high quality data from SEER database and competing risks model, which provided a guarantee for the accuracy of our study. However, inevitably, our research had some limitations. First, the established model is not comprehensive enough, because the SEER database does not include all prognostic factors for UTUC. Second, the data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans. Third, as an retrospective study, our results may be affected by confounding bias to some extent, so the conclusion needs to be further verified in future prospective studies. Fourth, the cause of death in SEER is that according to the death certificate report, some deaths may have been misclassified, which may also bring information bias to

our study.

Conclusions

In summary, this study used a competing-risks model to determine the prognostic factors for UTUC. The proportional subdistribution hazards model showed that sex, tumor size, surgery, distant metastasis, LNP, and LNR were associated with CSD, while LNE was not. The constructed nomogram can predict the 3, 5, and 8 years CSD probabilities of patients based on these relevant factors, which can support clinicians to make better judgments of the survival rates of individual patients.

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Footnotes

Contributorship statement: JL, CZL, and SZ designed the study; QH, DDH, and FSX collected and analyzed the data; CZL and XL drafted the initial manuscript; FFZ, and XJF reviewed and edited the article; All authors read and approved the final manuscript.

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Patient consent for publication: Not required.

Data availability statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement: The data analyses and use of the SEER database in our manuscript are in accordance with the DUA and do not require institutional review board approval or other ethics approval or consent of the study subjects.

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Table 1 The basic characteristics of the patients in this study.

Variables	Training Cohort	Validation Cohort	*p*
Number of Patients, n (%)	1803(70%)	773(30%)	
Age, Median (IQR)	71.00 (64.00, 78.00)	71.00 (63.00, 78.00)	0.710
Sex, n (%)			0.150
Female	711 (39.4)	329 (42.6)	
Male	1092 (60.6)	444 (57.4)	
Race, n (%)			0.045
Black	80 (4.4)	50 (6.5)	
Other	169 (9.4)	83 (10.7)	
White	1554 (86.2)	640 (82.8)	
Marital status, n (%)			0.656
Married	1565 (86.8)	677 (87.6)	
Others	67 (3.7)	31 (4.0)	
Single	171 (9.5)	65 (8.4)	
Year, n (%)			0.813
2004-2006	346 (19.2)	159 (20.6)	
2007-2009	439 (24.3)	181 (23.4)	
2010-2012	479 (26.6)	198 (25.6)	
2013-2015	539 (29.9)	235 (30.4)	
Site, n (%)			0.609
Renal pelvis	1152 (63.9)	485 (62.7)	
Ureter	651 (36.1)	288 (37.3)	
Grade, n (%)			0.481
Grade I	47 (2.6)	16 (2.1)	
Grade II	149 (8.3)	69 (8.9)	
Grade III	559 (31.0)	258 (33.4)	
Grade IV	1048 (58.1)	430 (55.6)	
Size, n (%)			0.188
[2,4)	559 (31.0)	268 (34.7)	
<2	262 (14.5)	106 (13.7)	
>=4	982 (54.5)	399 (51.6)	
Laterality, n (%)			0.551
Left	995 (55.2)	416 (53.8)	
Right	808 (44.8)	357 (46.2)	
Surgery, n (%)			0.203
NO/Unknown	9 (0.5)	8 (1.0)	
Yes	1794 (99.5)	765 (99.0)	
Radiotherapy, n (%)			0.931
NO/Unknown	1676 (93.0)	720 (93.1)	
Yes	127 (7.0)	53 (6.9)	
Chemotherapy, n (%)			0.938

NO/Unknown	1243 (68.9)	531 (68.7)	
Yes	560 (31.1)	242 (31.3)	
Distant metastasis, n (%)			0.053
M0	1652 (91.6)	689 (89.1)	
M1	151 (8.4)	84 (10.9)	
LNE, Median (IQR)	3.00 (1.00, 7.00)	3.00 (1.00, 7.00)	0.627
LNP, Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.542
LNR, Median (IQR)	0.00 (0.00, 0.50)	0.00 (0.00, 0.33)	0.546

Abbreviations: IQR, interquartile-range; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Table 2 The cumulative incidences of CSD and DOC among patients with UTUC.

Variables	Cancer-specific death (%)				Death due to other causes (%)			
	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	P	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	P
Age				<0.001				<0.001
Sex				<0.001				<0.001
Male	22.903(22.843-22.964)	27.131(27.064-27.197)	29.457(29.386-29.528)		25.697(25.634-25.760)	33.645(33.573-33.717)	40.755(40.673-40.837)	
Female	33.320(33.236-33.405)	38.157(38.066-38.247)	40.339(40.245-40.434)		18.710(18.639-18.780)	24.144(24.063-24.225)	29.031(28.937-29.125)	
Race				0.008				0.057
White	25.881(25.828-25.934)	29.921(29.864-29.979)	31.856(31.796-31.916)		23.502(23.451-23.554)	30.839(30.780-30.898)	37.596(37.528-37.664)	
Black	35.688(35.423-35.952)	44.479(44.194-44.763)	48.470(48.178-48.762)		22.782(22.555-23.009)	27.889(27.638-28.139)	30.253(29.987-30.519)	
Other	33.577(33.399-33.755)	39.945(39.752-40.138)	43.895(43.688-44.102)		17.728(17.586-17.869)	22.120(21.960-22.281)	25.822(25.642-26.003)	
Marital status				0.578				0.888
Married	26.658(26.605-26.711)	31.020(30.962-31.077)	33.378(33.317-33.440)		23.164(23.113-23.215)	30.048(29.990-30.106)	36.490(36.423-36.557)	
Single	28.974(28.808-29.140)	35.148(34.964-35.331)	37.145(36.956-37.334)		20.973(20.824-21.122)	28.420(28.246-28.593)	33.095(32.902-33.287)	
Others	30.406(30.132-30.681)	32.762(32.475-33.048)	32.762(32.475-33.048)		22.481(22.231-22.730)	30.490(30.186-30.794)	35.083(34.731-35.436)	
Year				0.430				0.535
2004-2006	27.535(27.424-27.646)	31.883(31.767-31.999)	33.622(33.505-33.739)		24.057(23.951-24.164)	32.174(32.058-32.290)	38.551(38.430-38.672)	
2007-2009	29.665(29.564-29.765)	34.035(33.930-34.139)	36.463(36.356-36.569)		22.606(22.513-22.698)	28.351(28.252-28.451)	34.151(34.045-34.256)	
2010-2012	26.033(25.940-26.126)	30.269(30.170-30.368)	—		21.838(21.751-21.926)	28.813(28.715-28.910)	—	
2013-2015	25.678(25.572-25.784)	—	—		23.766(23.661-23.871)	—	—	
Site				<0.001				0.161
Renal pelvis	30.986(30.921-31.051)	36.259(36.189-36.329)	38.503(38.430-38.577)		22.942(22.883-23.001)	28.605(28.539-28.672)	33.500(33.425-33.576)	
Ureter	19.946(19.870-20.021)	23.033(22.951-23.114)	25.368(25.279-25.456)		22.948(22.868-23.028)	32.131(32.037-32.225)	40.713(40.604-40.822)	
Grade				<0.001				0.043
Well	13.707(13.463-13.950)	13.707(13.463-13.950)	13.707(13.463-13.950)		18.635(18.356-18.914)	21.710(21.406-22.015)	40.163(39.717-40.609)	

Moderate	10.664(10.543-10.785)	13.393(13.255-13.530)	15.852(15.696-16.008)		10.147(10.028-10.267)	18.691(18.530-18.853)	27.546(27.340-27.752)	
Poor	30.407(30.315-30.498)	35.156(35.059-35.253)	37.336(37.236-37.437)		24.420(24.335-24.506)	30.727(30.633-30.822)	36.164(36.060-36.269)	
Undifferential	28.133(28.066-28.200)	33.013(32.939-33.086)	35.492(35.413-35.572)		24.207(24.142-24.271)	31.584(31.510-31.658)	37.338(37.252-37.424)	
Size				<0.001				0.733
<2	11.702(11.603-11.801)	15.012(14.896-15.129)	18.912(18.770-19.054)		23.698(23.568-23.828)	30.965(30.815-31.114)	41.203(41.019-41.386)	
[2,4)	20.339(20.257-20.421)	25.952(25.859-26.046)	27.404(27.307-27.501)		21.685(21.601-21.769)	29.655(29.556-29.754)	38.855(38.736-38.974)	
≥4	34.800(34.728-34.872)	38.868(38.792-38.944)	41.162(41.083-41.242)		23.457(23.393-23.521)	29.773(29.701-29.845)	33.440(33.361-33.519)	
Laterality				0.944				0.393
Left	26.970(26.903-27.037)	31.835(31.762-31.908)	33.636(33.560-33.713)		22.586(22.523-22.650)	29.551(29.479-29.624)	35.006(34.923-35.089)	
Right	27.092(27.017-27.167)	31.010(30.929-31.091)	33.867(33.781-33.954)		23.335(23.264-23.406)	30.305(30.223-30.387)	37.564(37.469-37.659)	
Surgery				0.001				0.980
Yes	26.715(26.665-26.765)	31.206(31.152-31.260)	33.490(33.432-33.547)		22.940(22.893-22.988)	29.950(29.895-30.004)	36.234(36.171-36.296)	
NO/Unknown	77.778(76.910-78.646)	—	—		22.222(21.522-22.923)	—	—	
Radiotherapy				<0.001				0.910
Yes	44.203(43.994-44.413)	50.407(50.191-50.623)	51.767(51.548-51.986)		25.971(25.788-26.155)	32.016(31.816-32.217)	34.632(34.422-34.842)	
NO/Unknown	25.670(25.619-25.721)	29.951(29.896-30.007)	32.292(32.233-32.351)		22.699(22.650-22.748)	29.733(29.677-29.789)	36.285(36.220-36.350)	
Chemotherapy				<0.001				0.003
Yes	36.276(36.177-36.375)	41.751(41.646-41.857)	43.283(43.175-43.391)		20.156(20.074-20.239)	26.807(26.711-26.903)	30.702(30.598-30.807)	
NO/Unknown	22.979(22.922-23.035)	27.032(26.970-27.094)	29.614(29.547-29.681)		24.177(24.119-24.235)	31.278(31.212-31.344)	38.534(38.457-38.611)	
Distant metastasis				<0.001				0.641
No	23.438(23.388-23.488)	28.067(28.012-28.122)	30.550(30.491-30.609)		22.674(22.624-22.723)	29.966(29.909-30.024)	36.800(36.734-36.866)	
Yes	65.586(65.407-65.765)	67.967(67.789-68.144)	67.967(67.789-68.144)		25.548(25.384-25.713)	28.750(28.577-28.922)	28.750(28.577-28.922)	
LNE	—	—	—	<0.001	—	—	—	0.941
LNP	—	—	—	<0.001	—	—	—	0.448
LNR	—	—	—	<0.001	—	—	—	<0.001

Abbreviations: CSD, cancer-specific death; DOC, death due to other causes; UTUC, upper-tract urothelial carcinoma;CI, confidence interval; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Table 3 Multivariate analysis by proportional subdistribution hazard model and cause-specific hazards model for CSD among patients with UTUC.

Variables	Proportional subdistribution hazards model				Cause-specific hazards model			
	Coefficient	sdHR	95%CI	*P*	Coefficient	csHR	95%CI	*P*
Age	-0.004	0.996	0.987-1.005	0.340	0.009	1.009	1.000-1.018	0.039
Sex								
Male	Reference				Reference			
Female	0.392	1.480	1.241-1.764	<0.001	0.301	1.351	1.134-1.611	<0.001
Race								
White	Reference				Reference			
Black	0.242	1.274	0.873-1.858	0.210	0.348	1.416	0.990-2.027	0.057
Other	0.201	1.223	0.930-1.607	0.150	0.164	1.178	0.899-1.544	0.235
Site								
Renal pelvis	Reference				Reference			
Ureter	-0.110	0.895	0.734-1.092	0.280	-0.106	0.899	0.732-1.105	0.313
Grade								
Well	Reference				Reference			
Moderate	-0.034	0.966	0.398-2.343	0.940	0.009	1.009	0.407-2.502	0.985
Poor	0.763	2.145	0.971-4.739	0.059	0.908	2.479	1.097-5.601	0.029
Undifferential	0.658	1.931	0.878-4.245	0.100	0.772	2.165	0.961-4.875	0.062
Size								
<2	Reference				Reference			
[2,4)	0.442	1.556	1.092-2.216	0.014	0.414	1.513	1.043-2.196	0.029
≥4	0.791	2.205	1.575-3.087	<0.001	0.881	2.414	1.691-3.447	<0.001
Surgery								
Yes	Reference				Reference			
NO/Unknown	0.791	2.205	1.292-3.761	0.004	0.752	2.120	0.990-4.539	0.053
Radiotherapy								

Yes	Reference				Reference			
NO/Unknown	-0.219	0.803	0.594-1.087	0.160	-0.240	0.787	0.595-1.040	0.092
Chemotherapy								
Yes	Reference				Reference			
NO/Unknown	0.025	1.025	0.829-1.269	0.820	0.171	1.187	0.972-1.450	0.093
Distant metastasis								
No	Reference				Reference			
Yes	0.881	2.414	1.842-3.163	<0.001	1.252	3.497	2.741-4.460	<0.001
LNE	-0.012	0.988	0.971-1.006	0.200	-0.013	0.987	0.972-1.002	0.091
LNP	0.062	1.064	1.022-1.107	0.002	0.069	1.072	1.032-1.113	<0.001
LNR	0.627	1.873	1.435-2.445	<0.001	0.934	2.544	1.965-3.294	<0.001

Abbreviations: CSD, cancer-specific death; UTUC, upper-tract urothelial carcinoma; sdHR, subdistribution hazard ratio; csHR, Cause-specific hazard ratio; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Figure legends

Figure 1. Data selection flowchart.

Figure 2. The CIF curves of CSD and DOC among UTUC patients.

Abbreviations: CIF, cumulative incidence function; CSD, cancer-specific death; DOC: death due to other causes; UTUC, upper-tract urothelial carcinoma.

Figure 3. Nomogram based on the competing risk analysis to predict CSD probabilities at 3, 5, and 8 years for UTUC patients.

Abbreviations: CSD, cancer-specific death; UTUC, upper-tract urothelial carcinoma; LNE: lymph nodes examined; LNP: lymph nodes positive.

Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years of the training (A, B, C) and validation (D, E, F) cohorts.

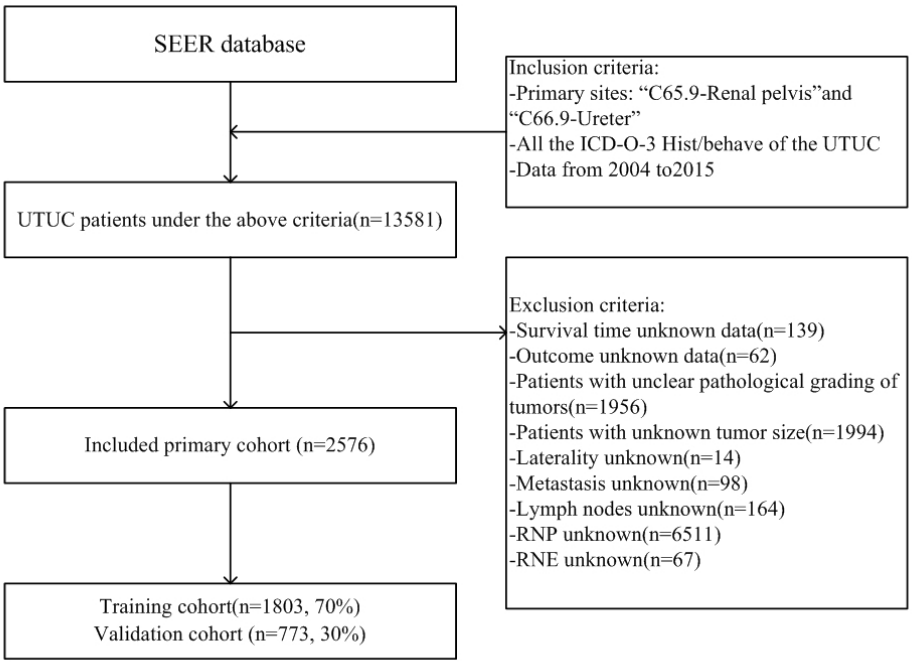

Figure 1. Data selection flowchart.

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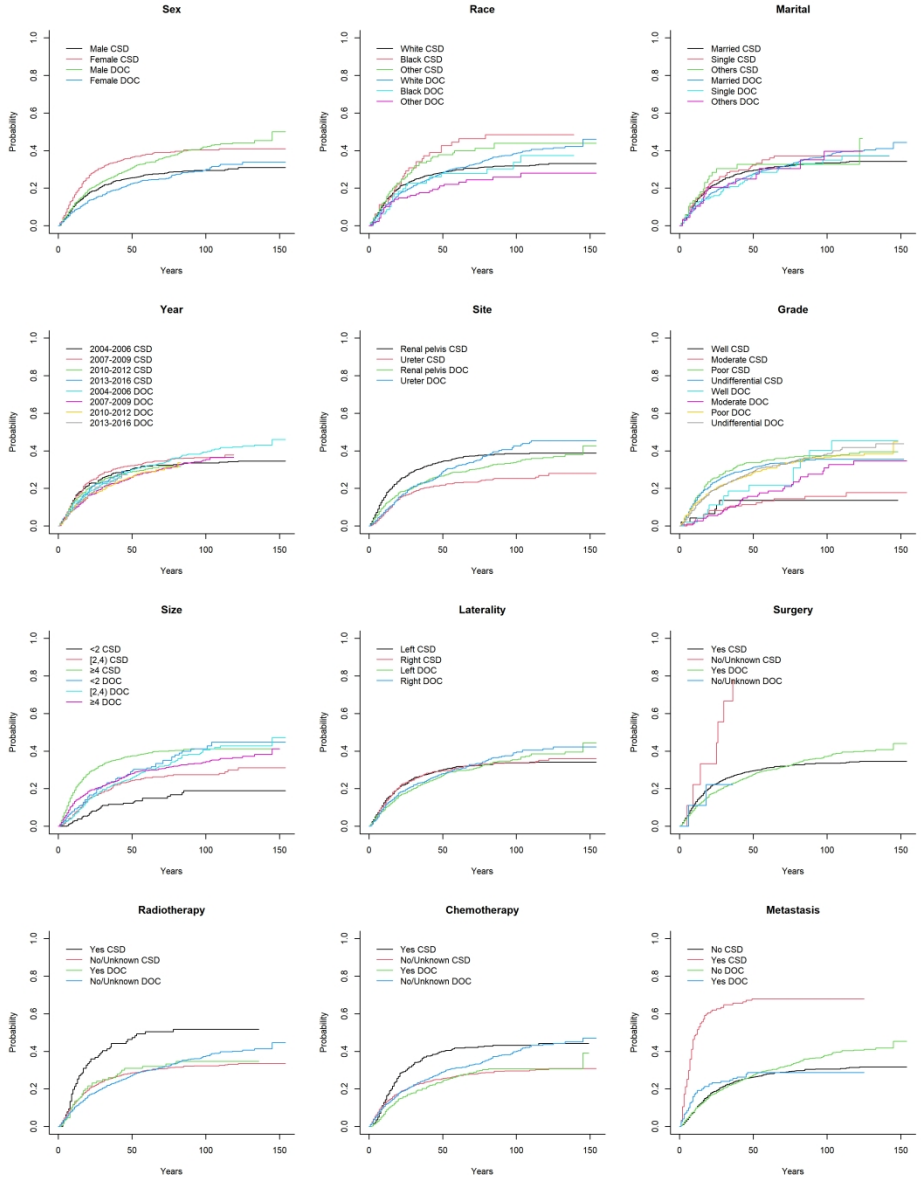

Figure 2. The CIF curves of CSD and DOC among UTUC patients.
Abbreviations: CIF, cumulative incidence function; CSD, cancer-specific death; DOC: death due to other causes; UTUC, upper-tract urothelial carcinoma.

296x381mm (300 x 300 DPI)

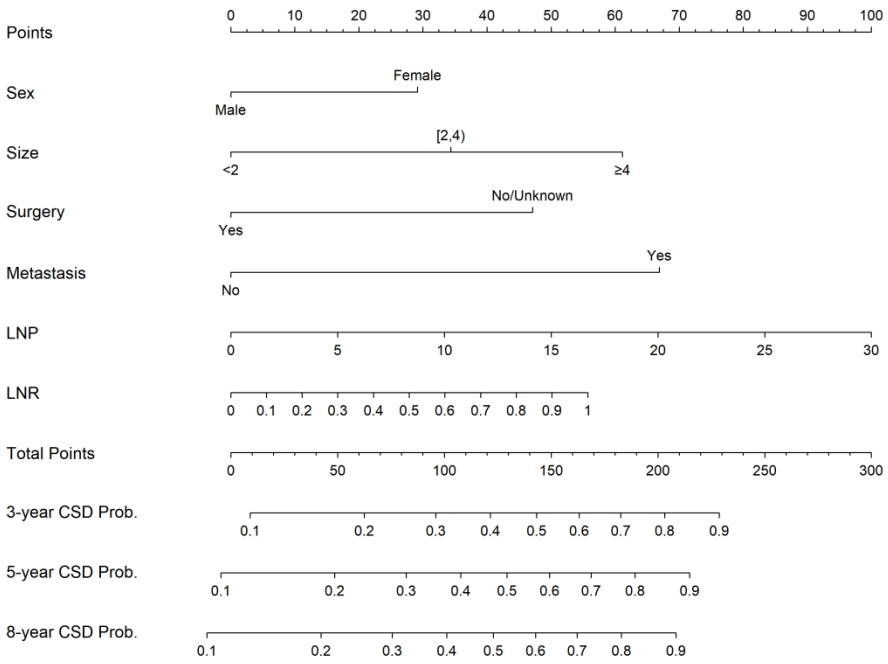

Figure 3. Nomogram based on the competing risk analysis to predict CSD probabilities at 3, 5, and 8 years for UTUC patients.
Abbreviations: CSD, cancer-specific death; UTUC, upper-tract urothelial carcinoma; LNE: lymph nodes examined; LNP: lymph nodes positive.

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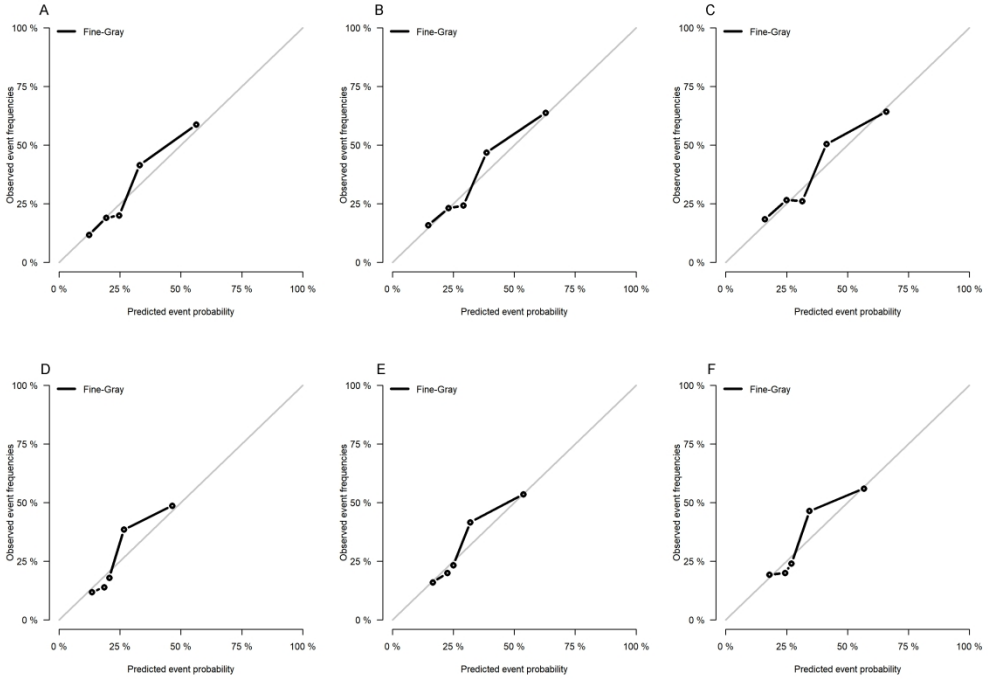

Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years of the training (A, B, C) and validation (D, E, F) cohorts.

296x211mm (300 x 300 DPI)

TRIPOD Checklist: Prediction Model Development

Section	Item	Checklist description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract				
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.		
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.		
Introduction				
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.		
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.		
Methods				
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, ifapplicable.		
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.		
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.		
	5b	Describe eligibility criteria for participants.		
	5c	Give details of treatments received, if relevant.		
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.		
	6b	Report any actions to blind assessment of the outcome to be predicted.		
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.		
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.		
Sample size	8	Explain how the study size was arrived at.		

Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.		
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.		
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.		
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.		
Risk groups	11	Provide details on how risk groups were created, if done.		
Results				
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.		
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.		
Model development	14a	Specify the number of participants and outcome events in each analysis.		
	14b	If done, report the unadjusted association between each candidate predictor and outcome.		
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).		
	15b	Explain how to the use the prediction model.		
Model performance	16	Report performance measures (with CIs) for the prediction model.		
Discussion				
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).		
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.		
Implications	20	Discuss the potential clinical use of the model and implications for future research.		
Other information				
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.		
Funding	22	Give the source of funding and the role of the funders for the present study.		

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A competing-risks nomogram for predicting cancer-specific death in upper-tract urothelial carcinoma: a population-based analysis

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A competing-risks nomogram for predicting cancer-specific death in upper-tract urothelial carcinoma: a population-based analysis

Running Head：Nomogram for UTUC cancer-specific death

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Abstract

Objectives: This study aimed to use a competing-risks model to establish a nomogram to accurately analyze the prognostic factors for upper tract urothelial carcinoma (UTUC) cancer-specific death (CSD).

Design: Retrospective observational cohort study.

Setting: The program has yielded a database of all cancer patients in 18 defined geographic regions of the United States.

Participants: We selected UTUC patients from the latest edition of the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2016. After excluding patients with unknown histological grade, tumor size, and lymph node status, finally 2576 patients were selected.

Primary and secondary outcome measures: We used the Fine-Gray proportional subdistribution hazards model for multivariate analysis and compared the results with cause-specific hazards model. We finally constructed a nomogram for the 3, 5, and 8 years CSD rates and tested these rates in a validation cohort.

Results: The proportional subdistribution hazards model showed that sex, tumor size, distant metastasis, surgery status, number of lymph nodes positive (LNP), and lymph nodes ratio (LNR) were independent prognostic factors for CSD. All significant factors associated with CSD were included in the nomogram. The 3-, 5-, and 8-years concordance indexes were 0.719, 0.702, and 0.692 in the training cohort, and 0.701, 0.675, and 0.668 in the validation cohort, respectively.

Conclusions: The competing-risks model showed that sex, tumor size, distant

metastasis, surgery status, LNP and LNR were associated with CSD. The nomogram predicts the probability of CSD in UTUC patients at 3, 5, and 8 years, which may help clinicians to predict the survival probabilities in individual patients.

Strengths and limitations of this study:

- The study established the first competing risk nomogram for predicting the 3-, 5-, and 8-year specific mortality probability for UTUC based on a large retrospective sample, which can improve the ability of clinicians to predict the survival probabilities in individual patients.
- The established model is not comprehensive enough, because the SEER database does not include all prognostic factors for UTUC.
- The data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans.
- The model requires prospective studies to confirm its reliability.

Keywords: competing risk model, upper-tract urothelial carcinoma(UTUC), nomogram, SEER, cancer-specific death

Abbreviations: UTUC: upper-tract urothelial carcinoma; CSD: cancer-specific death; DOC: death due to other causes; SEER: Surveillance, Epidemiology, and End Results; LNE: lymph nodes examined; LNP: lymph nodes positive; K-M: Kaplan-Meier; CIF: cumulative incidence function; ICD-O-3: International Classification of Diseases for Oncology-3; LNR: lymph nodes ratio; C-index: concordance index; CS: cause-specific hazards model; SD: proportional subdistribution hazards model

Introduction

Urothelial carcinomas are the fourth most common type of tumor [1], which is located in the upper or lower urinary tract. Upper-tract urothelial carcinoma (UTUC), including the renal pelvis and ureter carcinoma, currently accounts for 5% of urothelial malignancies [2]. The annual incidence of UTUC is typically estimated at 1 or 2 per 100,000 inhabitants in Western countries [3]. However, the increasing morbidity and mortality associated with UTUC [4, 5] are growing the importance of this research.

A previous study showed that UTUC has unique prognostic factors, which are different from bladder cancer and other urinary tract cancers [6]. Most studies analyzing the prognostic factors for UTUC have adopted the Kaplan-Meier (K-M) method or Cox regression methods [7–9]. These methods only consider a single endpoint while determining survival parameters. However, in clinical research, in addition to events of interest, there are often competing events. Competing events for cancer deaths refer to death from other causes unrelated to primary cancer, such as other diseases, car collisions, and suicide. In traditional survival analysis methods, these events were considered censored, making the cumulative incidence of cancer deaths overestimated. Applying standard survival analysis to competing-risks data leads to false and biased results [10]. Although the use of all-cause death as the study endpoint does not cause a competing risk bias, such an analysis cannot reflect the influence of factors on the specific endpoint of cancer death. Therefore, the

cumulative incidence function (CIF) of UTUC cancer-specific death (CSD) needs to be calculated, and prognostic factors for UTUC analyzed using the Fine-Gray proportional subdistribution hazards model [11].

A nomogram is based on a prognostic model and graphically represents the predictive abilities of different prognostic factors as the lengths of line segments. This format makes it easy for clinicians to make rapid and comprehensive decisions and predict the probability of CSD, which has great clinical significance. Some studies have constructed competing-risks nomograms for cancers such as sarcoma and prostate cancer [12, 13], but there is a lack of studies related to the UTUC.

The purpose of our research was to identify the prognostic factors of UTUC based on the competing risks model and used them to construct a nomogram to predict the survival rates of patients at the 3, 5, and 8 years.

Methods

Database and patients

The Surveillance, Epidemiology, and End Results (SEER) program has yielded a database of all cancer patients in 18 defined geographic regions of the United States collected by the National Cancer Institute. It is the largest cancer registry in the United States, including information on approximately 28% of the United States population. The SEER research data is publicly available; therefore, no informed consent or institutional review board approval is required when analyzing the data. We additionally requested chemotherapy data for inclusion in our research and obtained a license for using SEER software [14, 15].

We selected UTUC patients from the latest edition of the SEER database from 1975 to 2016. The primary sites were extracted using the SEER codes of "C65.9-Renal pelvis" and "C66.9-Ureter." Patients between 2004 and 2015 were included in the study. We included all of the histological subtypes of UTUC, according to the ICD-O-3 (third revision of the International Classification of Diseases for Oncology). The following demographic indicators were selected: age at diagnosis, sex, race, and marital status. The primary site, histological grade, tumor size, laterality, distant metastasis, surgery status, radiotherapy status, chemotherapy status, number of lymph nodes examined (LNE), lymph nodes positive (LNP), and lymph nodes ratio (LNR; calculated as the number of LNP divided by LNE) were also included as pathological characteristics. The tumor size was divided into three groups: <2, 2–4, and ≥4 cm [1, 16]. The study outcomes included CSD and death due to other causes (DOC). The survival time was reported in the available data in months.

Exclusion criteria

Our preliminary selection of the above methods initially identified 13,581 patients. Then, to ensure the study's accuracy, the exclusion criteria for the study data are as follows: unknown histological grade, unknown tumor size, and unknown lymph nodes status. The specific data selection process is shown in Figure 1. We finally chose 2576 patients for inclusion in follow-up investigations.

Figure 1

Statistical methods

We randomly divided the 2576 eligible patients into 2 groups using R software

(version 3.5.3, The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org): 70% (n=1803) in the training cohort and 30% (n=773) in the validation cohort. We first described the basic composition of each factor in the two patient cohorts using R software. The age, LNE, LNP and LNR were expressed as median and interquartile-range values, while categorical variables were represented as percentages. We evaluated differences in patient characteristics between two groups using the Student's t-test and Chi-square test.

We used the cumulative incidence function (CIF) to describe the probability of each event and also plotted the corresponding CIF curves. Moreover, Gray's test was used for univariate analysis to estimate the difference in CIF between groups. Significant variables ($P<0.05$) were included in the multivariate regression model. The Fine-Gray proportional sub-distribution hazards model was used for the multivariate analysis and compared with the results of the cause-specific hazards model. Applying the standard Cox regression method ignores the presence of competing risks and hence overestimates the actual incidence of beneficial events, leading to inappropriate risk stratification [17]. Several studies have confirmed that different approaches can be used in competing-risks settings for multivariate survival analysis. However, proportional subdistribution hazards model is the best method to predict the survival probability [18-20].

Finally, the results of Fine-Gray proportional sub-distribution hazards model were used to construct a nomogram of the 3, 5, and 8 years CSD rates. We used the concordance index (C-index) and calibration plots to evaluate the differentiation

ability and consistency of the established model in training and validation cohorts.

All statistical tests were conducted using R software (version 3.5.3). Probability values of $P<0.05$ were considered statistically significant, and all tests were two-sided. The SEER database can be accessed free of charge, and this study was exempted from obtaining informed consent.

Patients and public involvement

This study was conducted without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Moreover, patients were not allowed to contribute to the writing or editing of this document for readability or accuracy.

Results

Patient characteristics

The composition of each variable for the 2576 patients in the training and validation cohorts is presented in Table 1. The median age was 71 years in the training and validation cohorts, respectively. The majority of patients were male (60.6% and 57.4%), white (86.2% and 82.5%), and married (86.8% and 87.6%). The main UTUC sites were in the renal pelvis (63.9% and 62.7%, respectively, in the training and validation cohorts), with the rest in the ureter. The majority of patients were in the undifferentiated stage (58.1% and 55.6%), and most of the tumors in both cohorts were larger than 4 cm. Most patients in both cohorts had received surgery, whereas a few patients had received radiotherapy or chemotherapy. Only about 9% of patients had distant metastasis. The baseline characteristics of the training cohorts and

validation cohorts were similar.

Table 1

Univariate analysis

We calculated the 3-, 5-, and 8-years cumulative incidence rates of CSD and DOC. Year, laterality, and marital status were not related to either outcome (P>0.05), while age, sex, histological grade, chemotherapy status, and LNR were related to both outcomes (P<0.05). Race, primary site, tumor size, surgery status, radiotherapy status, distant metastasis, LNE, and LNP were significantly related to CSD. The corresponding CIF curves are shown in Figure 2. The cumulative incidence of CSD and DOC are compared in Table 2.

Figure 2, Table 2

Multivariate analysis

Table 3 shows the comparison of the proportional sub-distribution hazards model with the cancer-specific hazards model. The cancer-specific hazards model showed that sex, tumor size, distant metastasis, LNP and LNR were prognostic factors for UTUC (P<0.001). Then, we constructed the Fine-Gray proportional sub-distribution hazards model, indicating that sex (hazard ratio [HR]=1.480 for female, 95% confidence interval [CI]=1.241–1.764), tumor size (HR=1.556 for 2–4 cm, 95% CI=1.092–2.216; HR=2.205 for ≥4 cm, 95% CI=1.575–3.087), surgery status(HR=2.205 for no/unknown surgery, 95%CI=1.292-3.761), distant metastasis (HR=2.414 for distant, 95% CI=1.842-3.163), LNP(HR=1.064, 95%

CI=1.022-1.107), and LNR (HR=1.873, 95% CI=1.435-2.445) were prognostic factors affecting UTUC, as shown in Table 3.

Table 3

Construction and verification of the nomogram

Figure 3 shows the nomogram constructed according to the results of the Fine-Gray proportional subdistribution hazards model for predicting the CSD probabilities at 3, 5, and 8 years. LNP had the most significant impact on the probability of CSD, followed by distant metastasis, tumor size, LNR, surgery, and sex (Figure 3).

We used both the training and validation cohorts to verify the nomogram after establishing it. The 3-, 5-, and 8-years C-indexes were 0.719, 0.702, and 0.692 for the training cohort, respectively, and 0.701, 0.675, and 0.668 for the validation cohort. All of these values exceeded 0.6, indicating that the model had good discrimination ability. We then tested the prediction accuracy of the model. As shown in Figure 4, the 3-, 5-, and 8-years calibration plots for both cohorts were very close to the standard straight line, demonstrating that the model was well-calibrated.

Figures 3, 4

Discussion

The increasing incidence of UTUC [21] makes it necessary to further explore the prognostic factors for UTUC. The present study used a competing-risks model to accurately explore the prognostic factors for UTUC. It used these factors to construct a nomogram that provides clinicians with direct guidance while making relevant

decisions.

The application of study criteria resulted in the inclusion of 2576 patients from the SEER database, and 1542 of these patients died during the follow-up. However, only 750 of the deaths were related to UTUC. These results indicate that the number of DOC patients was almost the same as that for CSD. In this situation, if the traditional K-M or Cox survival analysis had been adopted, the DOC patients will be regarded as censored. This will lead to an overestimation of the cumulative incidence of CSD, which cannot truly reflect the prognosis [22, 23]. We overcame this shortcoming by using a competing risks model, which can adequately address the situation where the available data are related to multiple potential outcomes [24]. This method was first proposed by Fine and Gray and applied in previous studies [17,25–26]. In the case of competing risks, there are usually two models. One is the cause-specific hazards model (CS), the other is the proportional sub-distribution hazards model (SD), also known as the Fine-Gary model. In the present study, two models were analyzed and compared. CS is suitable for answering etiological questions, and SD is suitable for establishing clinical prediction models and risk scores. Therefore, we used the CIF and the proportional sub-distribution hazards model to explore the impact of various factors on the prognosis of CSD.

The univariate analysis results showed that age, sex, race, primary site, histological grade, tumor size, surgery status, radiotherapy status, chemotherapy status, distant metastasis, LNE, LNP, and LNR were influencing factors for CSD, while age, sex, histological grade, chemotherapy status, and LNR were influencing

factors for DOC. The cause-specific hazards model results showed that age, sex, histological grade, tumor size, distant metastasis, LNP, and LNR were prognostic factors for CSD. The proportional sub-distribution hazards model showed that sex, tumor size, surgery, distant metastasis, LNP, and LNR are independent prognostic factors for CSD.

Age is generally considered to be a prognostic factor for most cancers, and also for UTUC [27, 28]. Our CS model showed that age was a predictor of CSD; however, it was not statistically significant in the SD model. This may be because the effect of age on DOC is higher than the CSD; namely, elderly patients are more likely to die of other causes, which competitively leads to the fact that CSD incidence does not increase significantly with age. Sex and race have always been controversial prognostic factors. A previous study showed that race was a preoperative prognostic factor for UTUC patients [29]. Moreover, another study found no statistically significant differences in survival between males and females [30]. However, the competing-risks model in our study showed that sex was a risk factor for UTUC, while race was not. This may be because previous studies ignored the effect of competing risks. However, since most of the patients included in the SEER database are white; therefore, studies on different races need to be conducted.

Tumor size is also considered to be related to cancer prognosis. One study found 5-year recurrence-free survival rates for UTUC patients with tumor sizes <3 cm and ≥3 cm of 46.9% and 25.8%, respectively [31]. The univariate and multivariate analyses performed in the present study also indicated that tumor size was an

influencing factor for CSD. The prognosis was worse for tumors larger than 2 cm. In addition, our research also found that distant metastasis was an important risk factor for CSD. In terms of treatment methods, our study suggested that surgery status was a significant prognostic factor, which was consistent with the findings of Yuval et al. [32]. Surgery has long been considered the gold standard of UTUC treatment. However, radiotherapy status and chemotherapy status were not influencing factors for CSD in both competing risks models. This result conflicted with some previous findings, [33–35] suggesting that traditional Cox regression analysis overestimated the effects of radiotherapy and chemotherapy. Obviously, the relative lack of information on the radiotherapy status and chemotherapy status in the SEER database may also lead to inaccurate results, and thus further exploration of these indicators is needed.

Some indicators related to lymph nodes (e.g., distant lymph node metastasis, LNP, and LNE) are important clinical information for cancer prognosis, but whether they are independent prognostic factors for UTUC has not been determined. One study found that lymph node metastases were significantly associated with reduced cancer-specific survival in univariate analysis [36]. It is worth noting that very few studies have investigated LNP, LNE, and LNR. Our study is the first to use the SEER database to analyze the prognostic impact of these indicators on UTUC, and the results may be more accurate than those involving small samples. LNR is an emerging indicator that has been regarded as a prognostic factor in rectal cancer and breast cancer [37, 38]. Our results also suggested that LNR was an important prognostic

factor of UTUC. We found that LNE was an influencing factor for UTUC in the univariate analysis but not in the multivariate analysis. Moreover, both LNR and LNP entered the proportional sub-distribution hazards model, suggesting that after adjusting for the effects of LNR and LNP, LNE was no longer an independent prognostic indicator. LNP was a prognostic factor in all of the analyses, indicating that it significantly influences the prognosis of UTUC.

We utilized the results from the above-mentioned proportional sub-distribution hazards model to construct a nomogram that graphically represents the degrees of influence of various prognostic factors. This nomogram can be used to predict the 3-, 5-, and 8-years probabilities of CSD in UTUC patients. The predictive function of the nomogram has been used for different types of cancer and has even been proposed as a new standard. The nomogram is easy to use. In order to calculate the CSD probability of a UTUC patient, find the patient's sex (Male or Female) on the sex row, draw a vertical line on the dot row, and get the sex score value. Repeat the above steps for tumor size, M stage, surgery, LNP, and LNR. Add the score values of each variable, find the total point on the total point axis, and draw a straight downward line to get the 3, 5, and 8 years CSD probability of the UTUC patient. For example, a female (30 points), with a tumor size of 1.5cm (0 points), at M1 stage (68 points), had performed surgery (0 points), LNP equal to 5 (15 points), and LNR equal to 0.8 (45 points), the total score is 158 points, which corresponds to 3, 5, and 8 years CSD probability of 58%, 64%, and 69%, respectively.

The C-indexes for the nomogram all exceeded 0.6, demonstrating that the model

provided a good fit to the available data. The prediction calibration curves in Figure 4 were very close to the standard curve, indicating that the nomogram had good predictive ability. The results for the validation cohort also showed that the model was stable. Therefore, this model can help clinicians to quickly and easily determine the prognosis of individual patients and provide guidance in their clinical decision-making. However, the stability of the model needs further verification.

Our study used the large sample size and high-quality data from SEER database and competing risks model, which provided a guarantee for the accuracy of our study. However, inevitably, our research had some limitations. First, the established model is not comprehensive enough because the SEER database does not include all prognostic factors for UTUC. Second, the data available on the treatment status are not sufficiently detailed to distinguish the impact of various treatment plans. Third, as a retrospective study, our results may be affected by confounding bias to some extent, so the conclusion needs to be further verified in future prospective studies. Fourth, the cause of death in SEER is that some deaths may have been misclassified according to the death certificate report, which may also bring information bias to our study.

Conclusions

In summary, this study used a competing-risks model to determine the prognostic factors for UTUC. The proportional sub-distribution hazards model showed that sex, tumor size, surgery, distant metastasis, LNP, and LNR were associated with CSD, while LNE was not. The constructed nomogram can predict the 3, 5, and 8 years CSD probabilities of patients based on these relevant factors, which can support clinicians

to make better decisions of the survival rates of individual patients.

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Footnotes

Contributorship statement: JL, CZL, and SZ designed the study; QH, DDH, and FSX collected and analyzed the data; CZL and XL drafted the initial manuscript; FFZ, and XJF reviewed and edited the article; All authors read and approved the final manuscript.

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Patient consent for publication: Informed consent were not required in current study because SEER research data is publicly available and all patient data are de-identified.

Ethics statement: All procedures performed in the present study were in accordance with the principles outlined in the 1964 Helsinki Declaration and its later amendments. Institutional review board approval and informed consent were not required in current study because SEER research data is publicly available and all patient data are de-identified.

elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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Table 1 The basic characteristics of the patients in this study.

Variables	Training Cohort	Validation Cohort	*p*
Number of Patients, n (%)	1803(70%)	773(30%)	
Age, Median (IQR)	71.00 (64.00, 78.00)	71.00 (63.00, 78.00)	0.710
Sex, n (%)			0.150
Female	711 (39.4)	329 (42.6)	
Male	1092 (60.6)	444 (57.4)	
Race, n (%)			0.045
Black	80 (4.4)	50 (6.5)	
Other	169 (9.4)	83 (10.7)	
White	1554 (86.2)	640 (82.8)	
Marital status, n (%)			0.656
Married	1565 (86.8)	677 (87.6)	
Others	67 (3.7)	31 (4.0)	
Single	171 (9.5)	65 (8.4)	
Year, n (%)			0.813
2004-2006	346 (19.2)	159 (20.6)	
2007-2009	439 (24.3)	181 (23.4)	
2010-2012	479 (26.6)	198 (25.6)	
2013-2015	539 (29.9)	235 (30.4)	
Site, n (%)			0.609
Renal pelvis	1152 (63.9)	485 (62.7)	
Ureter	651 (36.1)	288 (37.3)	
Grade, n (%)			0.481
Grade I	47 (2.6)	16 (2.1)	
Grade II	149 (8.3)	69 (8.9)	
Grade III	559 (31.0)	258 (33.4)	
Grade IV	1048 (58.1)	430 (55.6)	
Size, n (%)			0.188
[2,4)	559 (31.0)	268 (34.7)	
<2	262 (14.5)	106 (13.7)	
>=4	982 (54.5)	399 (51.6)	
Laterality, n (%)			0.551
Left	995 (55.2)	416 (53.8)	
Right	808 (44.8)	357 (46.2)	
Surgery, n (%)			0.203
NO/Unknown	9 (0.5)	8 (1.0)	
Yes	1794 (99.5)	765 (99.0)	
Radiotherapy, n (%)			0.931
NO/Unknown	1676 (93.0)	720 (93.1)	
Yes	127 (7.0)	53 (6.9)	
Chemotherapy, n (%)			0.938

NO/Unknown	1243 (68.9)	531 (68.7)	
Yes	560 (31.1)	242 (31.3)	
Distant metastasis, n (%)			0.053
M0	1652 (91.6)	689 (89.1)	
M1	151 (8.4)	84 (10.9)	
LNE, Median (IQR)	3.00 (1.00, 7.00)	3.00 (1.00, 7.00)	0.627
LNP, Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.542
LNR, Median (IQR)	0.00 (0.00, 0.50)	0.00 (0.00, 0.33)	0.546

Abbreviations: IQR, interquartile-range; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Table 2 The cumulative incidences of CSD and DOC among patients with UTUC.

Variables	Cancer-specific death (%)				Death due to other causes (%)			
	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	P	3-Year (95%CI)	5-Year (95%CI)	8-Year (95%CI)	P
Age				<0.001				<0.001
Sex				<0.001				<0.001
Male	22.903(22.843-22.964)	27.131(27.064-27.197)	29.457(29.386-29.528)		25.697(25.634-25.760)	33.645(33.573-33.717)	40.755(40.673-40.837)	
Female	33.320(33.236-33.405)	38.157(38.066-38.247)	40.339(40.245-40.434)		18.710(18.639-18.780)	24.144(24.063-24.225)	29.031(28.937-29.125)	
Race				0.008				0.057
White	25.881(25.828-25.934)	29.921(29.864-29.979)	31.856(31.796-31.916)		23.502(23.451-23.554)	30.839(30.780-30.898)	37.596(37.528-37.664)	
Black	35.688(35.423-35.952)	44.479(44.194-44.763)	48.470(48.178-48.762)		22.782(22.555-23.009)	27.889(27.638-28.139)	30.253(29.987-30.519)	
Other	33.577(33.399-33.755)	39.945(39.752-40.138)	43.895(43.688-44.102)		17.728(17.586-17.869)	22.120(21.960-22.281)	25.822(25.642-26.003)	
Marital status				0.578				0.888
Married	26.658(26.605-26.711)	31.020(30.962-31.077)	33.378(33.317-33.440)		23.164(23.113-23.215)	30.048(29.990-30.106)	36.490(36.423-36.557)	
Single	28.974(28.808-29.140)	35.148(34.964-35.331)	37.145(36.956-37.334)		20.973(20.824-21.122)	28.420(28.246-28.593)	33.095(32.902-33.287)	
Others	30.406(30.132-30.681)	32.762(32.475-33.048)	32.762(32.475-33.048)		22.481(22.231-22.730)	30.490(30.186-30.794)	35.083(34.731-35.436)	
Year				0.430				0.535
2004-2006	27.535(27.424-27.646)	31.883(31.767-31.999)	33.622(33.505-33.739)		24.057(23.951-24.164)	32.174(32.058-32.290)	38.551(38.430-38.672)	
2007-2009	29.665(29.564-29.765)	34.035(33.930-34.139)	36.463(36.356-36.569)		22.606(22.513-22.698)	28.351(28.252-28.451)	34.151(34.045-34.256)	
2010-2012	26.033(25.940-26.126)	30.269(30.170-30.368)	—		21.838(21.751-21.926)	28.813(28.715-28.910)	—	
2013-2015	25.678(25.572-25.784)	—	—		23.766(23.661-23.871)	—	—	
Site				<0.001				0.161
Renal pelvis	30.986(30.921-31.051)	36.259(36.189-36.329)	38.503(38.430-38.577)		22.942(22.883-23.001)	28.605(28.539-28.672)	33.500(33.425-33.576)	
Ureter	19.946(19.870-20.021)	23.033(22.951-23.114)	25.368(25.279-25.456)		22.948(22.868-23.028)	32.131(32.037-32.225)	40.713(40.604-40.822)	
Grade				<0.001				0.043
Well	13.707(13.463-13.950)	13.707(13.463-13.950)	13.707(13.463-13.950)		18.635(18.356-18.914)	21.710(21.406-22.015)	40.163(39.717-40.609)	

Moderate	10.664(10.543-10.785)	13.393(13.255-13.530)	15.852(15.696-16.008)		10.147(10.028-10.267)	18.691(18.530-18.853)	27.546(27.340-27.752)	
Poor	30.407(30.315-30.498)	35.156(35.059-35.253)	37.336(37.236-37.437)		24.420(24.335-24.506)	30.727(30.633-30.822)	36.164(36.060-36.269)	
Undifferential	28.133(28.066-28.200)	33.013(32.939-33.086)	35.492(35.413-35.572)		24.207(24.142-24.271)	31.584(31.510-31.658)	37.338(37.252-37.424)	
Size				<0.001				0.733
<2	11.702(11.603-11.801)	15.012(14.896-15.129)	18.912(18.770-19.054)		23.698(23.568-23.828)	30.965(30.815-31.114)	41.203(41.019-41.386)	
[2,4)	20.339(20.257-20.421)	25.952(25.859-26.046)	27.404(27.307-27.501)		21.685(21.601-21.769)	29.655(29.556-29.754)	38.855(38.736-38.974)	
≥4	34.800(34.728-34.872)	38.868(38.792-38.944)	41.162(41.083-41.242)		23.457(23.393-23.521)	29.773(29.701-29.845)	33.440(33.361-33.519)	
Laterality				0.944				0.393
Left	26.970(26.903-27.037)	31.835(31.762-31.908)	33.636(33.560-33.713)		22.586(22.523-22.650)	29.551(29.479-29.624)	35.006(34.923-35.089)	
Right	27.092(27.017-27.167)	31.010(30.929-31.091)	33.867(33.781-33.954)		23.335(23.264-23.406)	30.305(30.223-30.387)	37.564(37.469-37.659)	
Surgery				0.001				0.980
Yes	26.715(26.665-26.765)	31.206(31.152-31.260)	33.490(33.432-33.547)		22.940(22.893-22.988)	29.950(29.895-30.004)	36.234(36.171-36.296)	
NO/Unknown	77.778(76.910-78.646)	—	—		22.222(21.522-22.923)	—	—	
Radiotherapy				<0.001				0.910
Yes	44.203(43.994-44.413)	50.407(50.191-50.623)	51.767(51.548-51.986)		25.971(25.788-26.155)	32.016(31.816-32.217)	34.632(34.422-34.842)	
NO/Unknown	25.670(25.619-25.721)	29.951(29.896-30.007)	32.292(32.233-32.351)		22.699(22.650-22.748)	29.733(29.677-29.789)	36.285(36.220-36.350)	
Chemotherapy				<0.001				0.003
Yes	36.276(36.177-36.375)	41.751(41.646-41.857)	43.283(43.175-43.391)		20.156(20.074-20.239)	26.807(26.711-26.903)	30.702(30.598-30.807)	
NO/Unknown	22.979(22.922-23.035)	27.032(26.970-27.094)	29.614(29.547-29.681)		24.177(24.119-24.235)	31.278(31.212-31.344)	38.534(38.457-38.611)	
Distant metastasis				<0.001				0.641
No	23.438(23.388-23.488)	28.067(28.012-28.122)	30.550(30.491-30.609)		22.674(22.624-22.723)	29.966(29.909-30.024)	36.800(36.734-36.866)	
Yes	65.586(65.407-65.765)	67.967(67.789-68.144)	67.967(67.789-68.144)		25.548(25.384-25.713)	28.750(28.577-28.922)	28.750(28.577-28.922)	
LNE	—	—	—	<0.001	—	—	—	0.941
LNP	—	—	—	<0.001	—	—	—	0.448
LNR	—	—	—	<0.001	—	—	—	<0.001

Abbreviations: CSD, cancer-specific death; DOC, death due to other causes; UTUC, upper-tract urothelial carcinoma;CI, confidence interval; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Table 3 Multivariate analysis by proportional subdistribution hazard model and cause-specific hazards model for CSD among patients with UTUC.

Variables	Proportional subdistribution hazards model				Cause-specific hazards model			
	Coefficient	sdHR	95%CI	*P*	Coefficient	csHR	95%CI	*P*
Age	-0.004	0.996	0.987-1.005	0.340	0.009	1.009	1.000-1.018	0.039
Sex								
Male	Reference				Reference			
Female	0.392	1.480	1.241-1.764	<0.001	0.301	1.351	1.134-1.611	<0.001
Race								
White	Reference				Reference			
Black	0.242	1.274	0.873-1.858	0.210	0.348	1.416	0.990-2.027	0.057
Other	0.201	1.223	0.930-1.607	0.150	0.164	1.178	0.899-1.544	0.235
Site								
Renal pelvis	Reference				Reference			
Ureter	-0.110	0.895	0.734-1.092	0.280	-0.106	0.899	0.732-1.105	0.313
Grade								
Well	Reference				Reference			
Moderate	-0.034	0.966	0.398-2.343	0.940	0.009	1.009	0.407-2.502	0.985
Poor	0.763	2.145	0.971-4.739	0.059	0.908	2.479	1.097-5.601	0.029
Undifferential	0.658	1.931	0.878-4.245	0.100	0.772	2.165	0.961-4.875	0.062
Size								
<2	Reference				Reference			
[2,4)	0.442	1.556	1.092-2.216	0.014	0.414	1.513	1.043-2.196	0.029
≥4	0.791	2.205	1.575-3.087	<0.001	0.881	2.414	1.691-3.447	<0.001
Surgery								
Yes	Reference				Reference			
NO/Unknown	0.791	2.205	1.292-3.761	0.004	0.752	2.120	0.990-4.539	0.053
Radiotherapy								

Yes	Reference				Reference			
NO/Unknown	-0.219	0.803	0.594-1.087	0.160	-0.240	0.787	0.595-1.040	0.092
Chemotherapy								
Yes	Reference				Reference			
NO/Unknown	0.025	1.025	0.829-1.269	0.820	0.171	1.187	0.972-1.450	0.093
Distant metastasis								
No	Reference				Reference			
Yes	0.881	2.414	1.842-3.163	<0.001	1.252	3.497	2.741-4.460	<0.001
LNE	-0.012	0.988	0.971-1.006	0.200	-0.013	0.987	0.972-1.002	0.091
LNP	0.062	1.064	1.022-1.107	0.002	0.069	1.072	1.032-1.113	<0.001
LNR	0.627	1.873	1.435-2.445	<0.001	0.934	2.544	1.965-3.294	<0.001

Abbreviations: CSD, cancer-specific death; UTUC, upper-tract urothelial carcinoma; sdHR, subdistribution hazard ratio; csHR, Cause-specific hazard ratio; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.

Figure legends

Figure 1. Data selection flowchart.

Figure 2. The CIF curves of CSD and DOC among UTUC patients.

Abbreviations: CIF, cumulative incidence function; CSD, cancer-specific death; DOC: death due to other causes; UTUC, upper-tract urothelial carcinoma.

Figure 3. Nomogram based on the competing risk analysis to predict CSD probabilities at 3, 5, and 8 years for UTUC patients.

Abbreviations: CSD, cancer-specific death; UTUC, upper-tract urothelial carcinoma; LNE: lymph nodes examined; LNP: lymph nodes positive.

Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years of the training (A, B, C) and validation (D, E, F) cohorts.

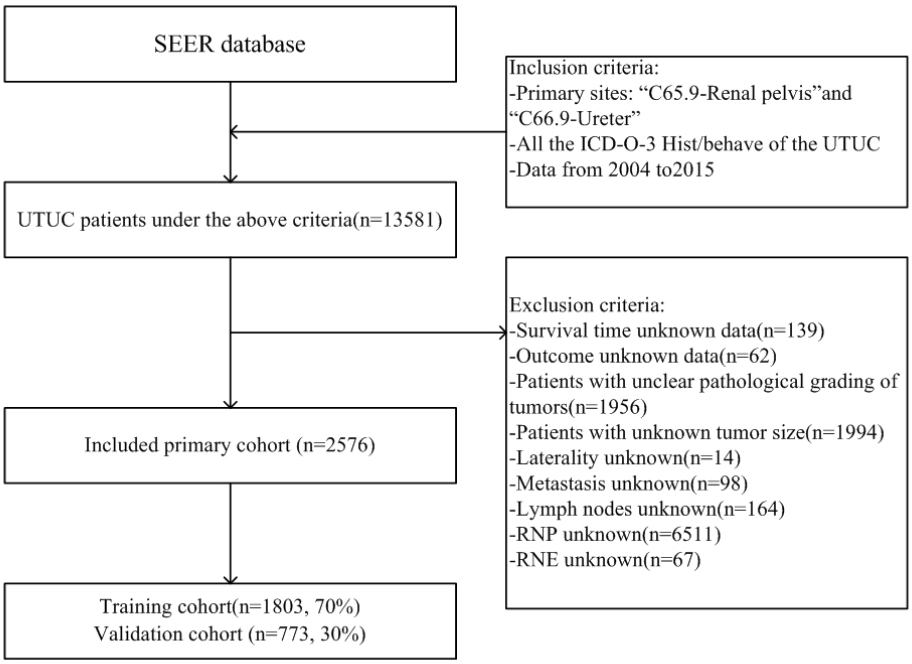

Figure 1. Data selection flowchart.

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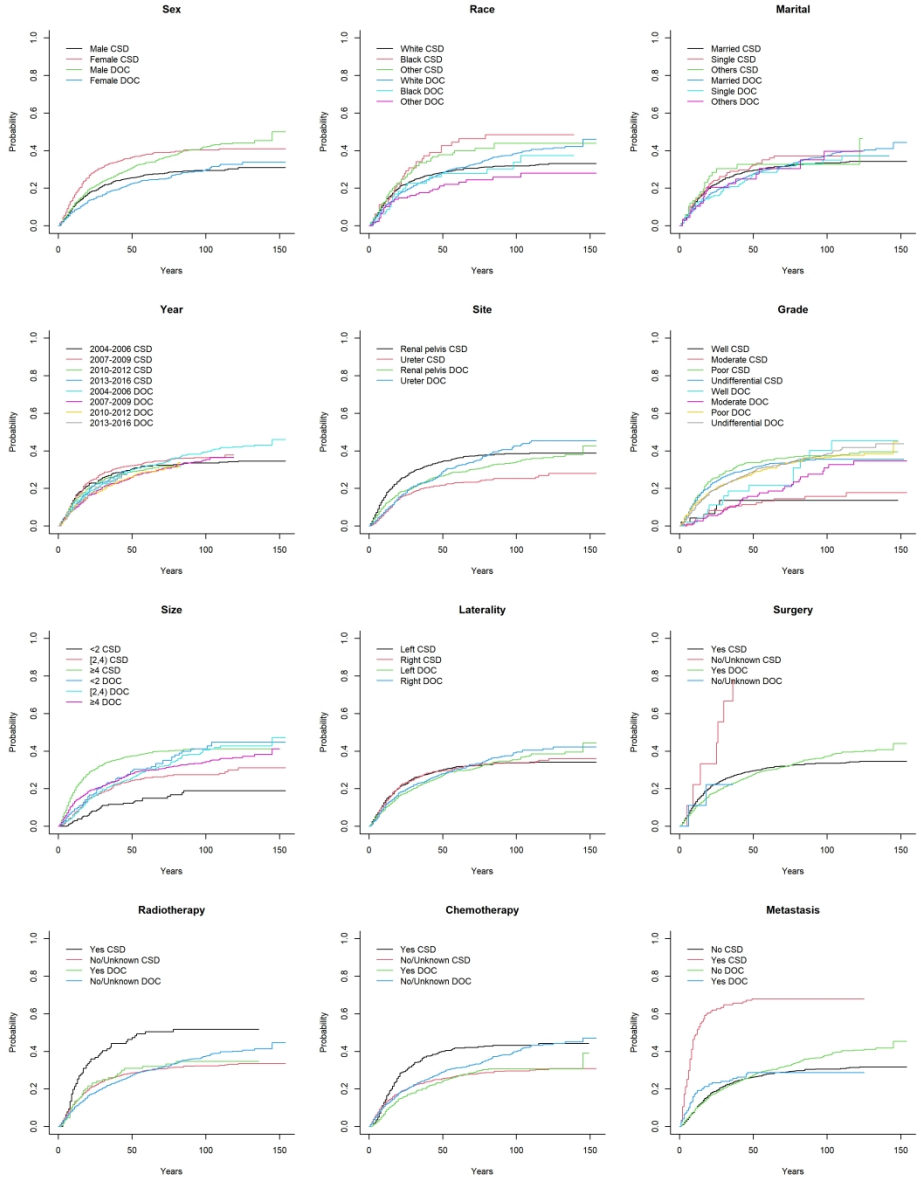

Figure 2. The CIF curves of CSD and DOC among UTUC patients.
Abbreviations: CIF, cumulative incidence function; CSD, cancer-specific death; DOC: death due to other causes; UTUC, upper-tract urothelial carcinoma.

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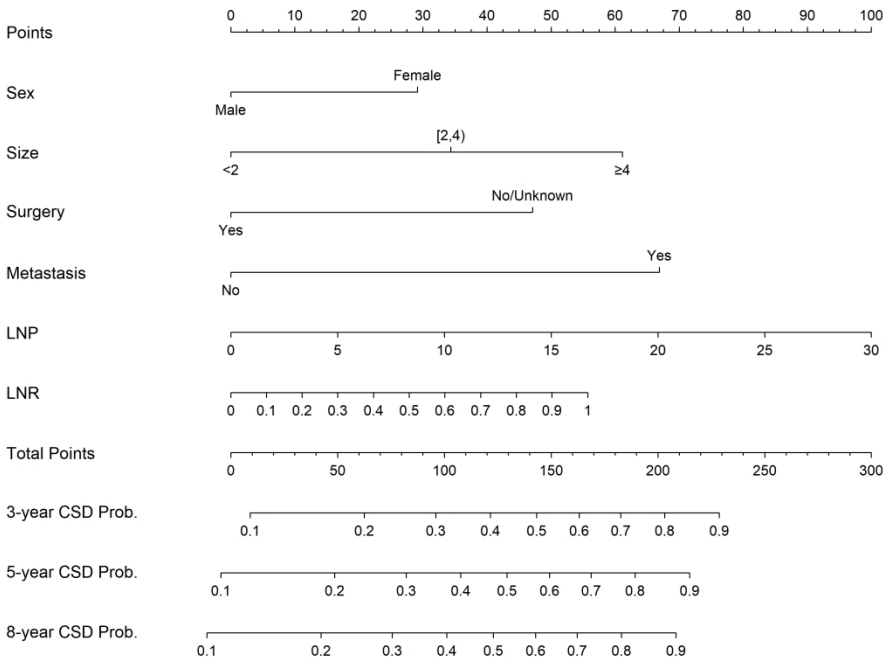

Figure 3. Nomogram based on the competing risk analysis to predict CSD probabilities at 3, 5, and 8 years for UTUC patients.
Abbreviations: CSD, cancer-specific death; UTUC, upper-tract urothelial carcinoma; LNE: lymph nodes examined; LNP: lymph nodes positive.

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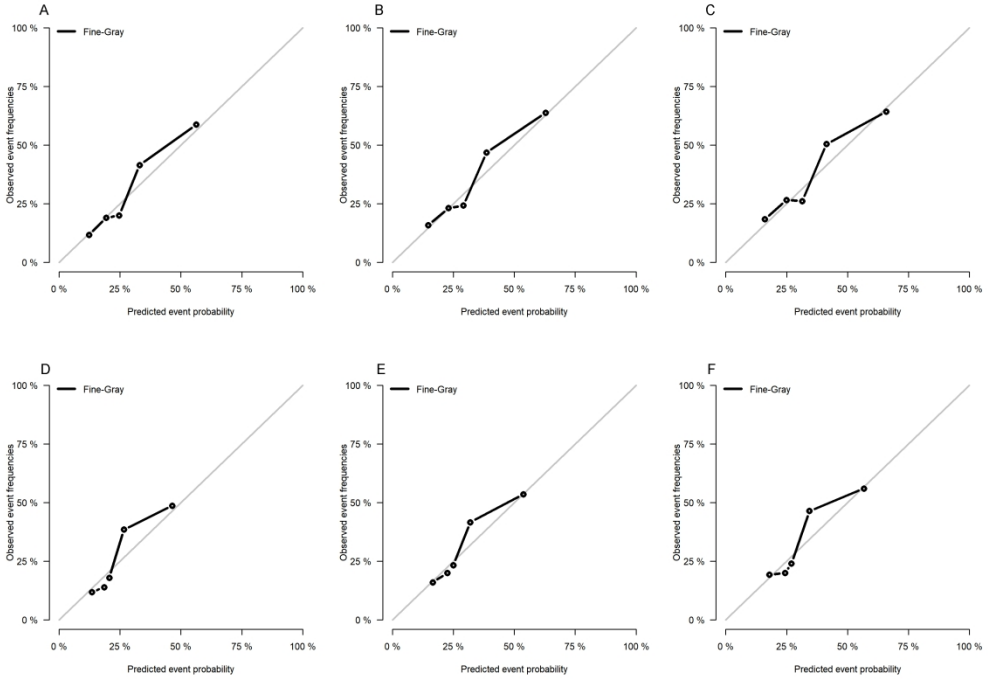

Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years of the training (A, B, C) and validation (D, E, F) cohorts.

296x211mm (300 x 300 DPI)

TRIPOD Checklist: Prediction Model Development

Section	Item	Checklist description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract				
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.		
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.		
Introduction				
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.		
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.		
Methods				
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, ifapplicable.		
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.		
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.		
	5b	Describe eligibility criteria for participants.		
	5c	Give details of treatments received, if relevant.		
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.		
	6b	Report any actions to blind assessment of the outcome to be predicted.		
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.		
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.		
Sample size	8	Explain how the study size was arrived at.		

Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.		
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.		
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.		
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.		
Risk groups	11	Provide details on how risk groups were created, if done.		
Results				
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.		
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.		
Model development	14a	Specify the number of participants and outcome events in each analysis.		
	14b	If done, report the unadjusted association between each candidate predictor and outcome.		
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).		
	15b	Explain how to the use the prediction model.		
Model performance	16	Report performance measures (with CIs) for the prediction model.		
Discussion				
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).		
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.		
Implications	20	Discuss the potential clinical use of the model and implications for future research.		
Other information				
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.		
Funding	22	Give the source of funding and the role of the funders for the present study.