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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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4 **A competing-risks nomogram for predicting cancer-specific death in**
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6 **upper-tract urothelial carcinoma: a population-based analysis**
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11 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

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4 probability of CSD in UTUC patients at 3, 5, and 8 years, which can improve the
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6 ability of clinicians to predict the survival probabilities in individual patients.
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10 11 **Strengths and limitations of this study:**

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14 •The study established the first competing risk nomogram for predicting the 3-, 5-,
15
16 and 8-year specific mortality probability for UTUC based on a large retrospective
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18 sample, which can improve the ability of clinicians to predict the survival
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20 probabilities in individual patients.
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24 •The established model is not comprehensive enough, because the SEER database
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26 does not include all prognostic factors for UTUC.
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30 •The data available on the treatment status are not sufficiently detailed to distinguish
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32 the impact of various treatment plans.
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36 •The model requires prospective studies to confirm its reliability.
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41 **Keywords:** competing risk model, upper-tract urothelial carcinoma, nomogram,
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43 SEER, cancer-specific death
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48 **Introduction**

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

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

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40 The purpose of our research is to identify the prognostic factors of UTUC and
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42 used them to construct a nomogram to predict the survival rates of patients at the 3, 5,
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44 and 8 years. A nomogram is based on a prognostic model and graphically presents the
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46 predictive abilities of different prognostic factors as the lengths of line segments. This
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48 format makes it easy for clinicians to make rapid and comprehensive judgments and
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4 to predict the probability of CSD, which has great clinical significance. Some studies
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6 have constructed competing-risks nomograms for cancers such as sarcoma and
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8 prostate cancer,[12, 13] but research related to UTUC has been lacking.
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11 The current study was conducted to assess the effect of several factors in UTUC
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13 using a competing-risks method, and to construct a comprehensive nomogram that
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15 presents the impacts of these prognostic factors in order to guide clinical work.
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19 **Methods**

20 Database and patients

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22 The Surveillance, Epidemiology, and End Results (SEER) program has yielded a
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24 database of all cancer patients in 18 defined geographic regions of the United States
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26 collected by the National Cancer Institute. It is the largest cancer registry in the
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28 United States and includes information on approximately 28% of the United States
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30 population. Because part of the SEER research data is publicly available, no informed
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32 consent or institutional review board approval is required when analyzing the data.
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34 We additionally requested chemotherapy data for inclusion in our research and
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36 obtained a license for using SEER software.[14, 15]
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45 We selected UTUC patients from the latest edition of the SEER database that
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47 covers from 1975 to 2016. The primary sites were extracted using the SEER codes of
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49 “C65.9-Renal pelvis” and “C66.9-Ureter.” We included all of the histological
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51 subtypes of UTUC, according to the ICD-O-3 (third revision of the International
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53 Classification of Diseases for Oncology). The following demographic indicators were
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55 selected: age at diagnosis, sex, race, and marital status. Primary site, histological
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4 grade, tumor size, laterality, distant metastasis, surgery status, radiotherapy status,
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6 chemotherapy status, number of lymph nodes examined (LNE), lymph nodes positive
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8 (LNP), and lymph nodes ratio (LNR; calculated as the number of LNP divided by
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10 LNE) were also included as pathological characteristics. We divided the ages into
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12 four groups: 20–40, 40–60, 60–80, and >80 years. The tumor size was categorized
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14 into three groups: <2, 2–4, and ≥4 cm.[1, 16] The study outcomes included survival,
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16 CSD, and death due to other causes (DOC). The survival time was reported in the
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18 available data in months.
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24 Exclusion criteria

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27 Our preliminary selection of the above methods initially identified 13,581
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29 patients. Then, in order to ensure the accuracy of the study, the exclusion criteria for
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31 the study data are as follows: unknown histological grade, unknown tumor size, and
32
33 unknown lymph nodes status. The specific data selection process is shown in
34
35 Figure 1. We finally chose 2576 patients for inclusion in follow-up investigations.
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40 Figure 1

41 42 43 Statistical methods

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45 We randomly divided the 2576 eligible patients into 2 groups using R software
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47 (version 3.5.3, The R Foundation for Statistical Computing, Vienna, Austria;
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49 <http://www.r-project.org>): 70% (n=1803) in the training cohort and 30% (n=773) in
50
51 the validation cohort. We first described the basic composition of each factor in the
52
53 two patient cohorts using SPSS software (version 23.0, Armonk, NY: IBM Corp). The
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55 LNR was expressed as median and interquartile-range values, while categorical
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4 variables were represented as percentages.
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7 In a univariate analysis, R software was used to calculate the CIF to describe the
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9 probability of death, while SAS software (SAS Institute, USA) was used to implement
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11 Gray's test to determine the difference in CIF between each variable group. We then
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13 performed a multivariate analysis using SAS. We used the Fine-Gray subdistribution
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15 proportional-hazards model for the multivariate analysis and compared the results
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17 with using traditional Cox proportional-hazards models. Applying the standard Cox
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19 regression method ignores the presence of competing risks and hence overestimates
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21 the actual incidence of beneficial events, and so may lead to inappropriate risk
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23 stratification.[17] Several studies have confirmed that different approaches can be
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25 used in competing-risks settings for multivariate survival analysis, but subdistribution
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27 proportional-hazards model have been found to be the best predictors of survival
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29 probability.[18]
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38 Finally, the multivariate analysis results were used to construct a nomogram of
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40 the 3, 5, and 8 years CSD rates, which was tested using the validation cohort. We used
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42 the concordance index (C-index) and calibration plots to evaluate the differentiation
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44 ability and consistency of the established model.
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49 All statistical tests were conducted using SPSS (version 23), R software
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51 (version 3.5.3), and SAS (version 9.4). Probability values of $P < 0.05$ were considered
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53 statistically significant, and all tests were two-sided. The SEER database can be
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55 accessed free of charge, and this study was exempted from obtaining informed
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57 consent.
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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

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4 median LNRs were 0.00 (range, 0.00–0.46) and 0.00 (range, 0.00–0.36), respectively.
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6 Table 1
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8 9 Univariate analysis

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11 We calculated the 3, 5, and 8 years cumulative incidence rates of CSD and DOC.
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13 Laterality and marital status were not related to either outcome ($P>0.05$), while sex,
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15 race, histological grade, chemotherapy status, LNP, and LNR were related to both
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17 outcomes ($P<0.05$). Age was significantly related to DOC, while primary site, tumor
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19 size, surgery status, radiotherapy status, distant metastasis, and LNE were
20
21 significantly related to CSD. The CIF curves of variables specifically related to CSD
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23 are shown in Figure 2, while other figures are provided in Appendix 1. The
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25 cumulative incidence rates of CSD and DOC are compared in Table 2.
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32 Figure 2, Table 2
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34 35 36 37 38 Multivariate analysis

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40 Our comparison of the competing-risks model with a traditional Cox regression
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42 model yielded the results presented in Table 3. The Cox regression model showed that
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44 tumor size, chemotherapy status, distant metastasis, and LNP were prognostic factors
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46 for UTUC ($P<0.001$). We then constructed the Fine-Gray subdistribution
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48 proportional-hazards model. The multivariate competing-risks analysis indicated that
49
50 sex (hazard ratio [HR]=1.308 for female, 95% confidence interval [CI]=1.093–1.564),
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52 race (HR=1.670 for other races, 95% CI=1.290–2.162), tumor size (HR=1.656 for 2–
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54 4 cm, 95% CI=1.161–2.363; HR=2.065 for ≥ 4 cm, 95% CI=1.461–2.918), distant
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4 metastasis (HR=2.233 for distant, 95% CI=1.706–2.923), LNE (HR=0.711 for 4–7
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6 lymph nodes, 95% CI=0.545–0.928; HR=0.698 for ≥ 8 lymph nodes, 95% CI=0.540–
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8 0.903), and LNP (HR=2.252, 95% CI=1.580–3.211) were prognostic factors affecting
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10 UTUC, as presented in Table 3.
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Table 3

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20 Construction and verification of the nomogram

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22 Figure 3 shows the nomogram we constructed according to the results of the
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24 multivariate competing-risks analysis for predicting the CSD probabilities at 3, 5, and
25
26 8 years. The figure shows that LNP had the greatest impact on the probability of CSD,
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28 followed by distant metastasis, tumor size, race, LNE, and sex.
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32 We used the validation cohort to verify the nomogram after establishing it. The 3,
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34 5, and 8 years C-indexes were 0.723, 0.707, and 0.696 for the training cohort,
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36 respectively, and 0.708, 0.702, and 0.701 for the validation cohort. All of these values
37
38 exceed 0.6, which indicates that the model has good discrimination ability. We then
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40 tested the prediction accuracy of the model. As shown in Figure 4, the 3, 5, and 8
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42 years calibration plots for both cohorts were very close to the standard straight line,
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44 demonstrating that the model was well calibrated.
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Figures 3, 4

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56 Discussion

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58 The increasing incidence of UTUC[19] makes it necessary to further explore the
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4 prognostic factors for UTUC. The present study used a competing-risks model to
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6 more accurately explore the prognostic factors for UTUC, and used these factors to
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8 construct a nomogram to provide clinicians with direct guidance when they are
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10 making relevant predictions.
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14 The application of study criteria resulted in the inclusion in 2576 patients from
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16 the SEER database, and 1542 of these patients died during the follow-up, although
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18 only 750 of the deaths were related to UTUC. This means that the number of DOC
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20 patients was almost the same as that for CSD. In this situation, if the traditional K-M
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22 or Cox survival analysis had been adopted, both death outcomes would have been
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24 considered to be related to UTUC.[20, 21] This would overestimate the proportion of
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26 CSD patients and hence not truly reflect the prognosis of CSD. We overcame this
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28 shortcoming by using a subdistribution proportional-hazards model, which can
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30 properly address the situation where the available data are related to multiple potential
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32 outcomes.[22] This method was first proposed by Fine and Gray, and has also been
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34 applied in some previous studies.[23–25] In the presence of competing risks, we used
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36 the CIF and the subdistribution proportional-hazards model to explore the impact of
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38 various factors on CSD.
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48 The univariate analysis results showed that sex, race, primary site, histological
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50 grade, tumor size, surgery status, radiotherapy status, chemotherapy status, distant
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52 metastasis, LNE, LNP, and LNR are influencing factors for CSD, while age, sex, race,
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54 histological grade, chemotherapy status, LNP, and LNR are influencing factors for
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56 DOC. The multivariate Cox regression model results showed that tumor size, distant
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4 metastasis, chemotherapy status, and LNP are prognostic factors for CSD. The
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6 subdistribution proportional-hazards model showed that sex, race, tumor size, distant
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8 metastasis, LNE, and LNP are independent prognostic factors for CSD.
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11 Age is a prognostic factor for most cancers, and this has also found to be the case
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13 for CSD.[26, 27] However, our univariate analysis results showed that age is only a
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15 prognosis factor for DOC, and the multivariate analysis did not include age as a
16
17 variable, indicating that age is not a separate prognosis factor for UTUC. Previous
18
19 studies may have ignored competing events, and sex and race have always been
20
21 controversial prognostic factors. One study showed that age and race are preoperative
22
23 prognostic factors for UTUC patients.[28] In contrast, another study found no
24
25 statistically significant differences in survival between males and females.[29] The
26
27 competing-risks model in our study showed that sex and race are risk factors for
28
29 UTUC. However, since most of the patients included in the SEER database are white,
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31 the results regarding race need to be further validated.
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40 Tumor size has always been a prognostic factor. One study found 5-year
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42 recurrence-free survival rates for patients with tumor sizes <3 cm and ≥ 3 cm of 46.9%
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44 and 25.8%, respectively.[30] The univariate and multivariate analyses performed in
45
46 the present study indicated that tumor size is an influencing factor for CSD, with the
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48 prognosis being worse for tumors larger than 2 cm. In terms of treatment methods,
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50 surgery status, radiotherapy status, and chemotherapy status were not influencing
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52 factors for CSD in the subdistribution proportional-hazards model. This conflicts with
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54 some previous findings,[31–33] suggesting that traditional Cox regression analysis
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4 overestimates the effects of surgery, radiotherapy, and chemotherapy. Of course, the
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6 relative lack of information on the radiotherapy status and chemotherapy status in the
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8 SEER database may also lead to inaccurate results, and so further exploration of these
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10 indicators is needed.
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14 Some indicators related to lymph nodes (e.g., distant lymph node metastasis,
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16 LNP, and LNE) have been found to be important clinical information for the
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18 prognosis of cancer, but whether they are independent prognostic factors for UTUC
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20 has not been determined. One study found that lymph node metastases were
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22 significantly associated with reduced disease-specific survival in univariate
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24 analysis.[34] Our research also found that distant metastasis is an important
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26 prognostic factor for CSD, in both the univariate and multivariate analyses.
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32 It is worth noting that very few studies have investigated LNP, LNE, and LNR.
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34 Our study is the first to use the SEER database to analyze the prognostic impact of
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36 these indicators on UTUC, and the results may be more accurate than those of studies
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38 involving small samples. LNR is an emerging indicator that has been regarded as a
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40 prognostic factor in rectal cancer and breast cancer.[35, 36] We found that LNR was
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42 an influencing factor for UTUC in the univariate analysis but not in the multivariate
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44 analysis. Moreover, both LNE and LNP entered the subdistribution
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46 proportional-hazards model, which showed that after adjusting for the effects of LNE
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48 and LNP, LNR was no longer an independent prognostic indicator. After excluding
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50 competing events, LNE was an independent prognostic factor for UTUC. It can be
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52 seen from the results that a higher LNE decreases the probability of CSD. However,
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4 LNE did not influence DOC. This shows that LNE is more specific for UTUC, and so
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6 more attention should be paid to its role as a prognostic factor for UTUC patients in
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8 the future. LNP was a prognostic factor in all of the analyses, indicating that it greatly
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10 influences the prognosis of UTUC.
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14 We utilized the results from the above-mentioned subdistribution
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16 proportional-hazards model to construct a nomogram that graphically presents the
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18 degrees of influence of various prognostic factors. This nomogram also integrates
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20 various indicators to predict the 3, 5, and 8 years probabilities of CSD. The C-indexes
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22 for the nomogram all exceeded 0.6, demonstrating that the model provides a good fit
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24 to the available data. The prediction calibration curves in Figure 4 are very close to
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26 the standard curve, which indicates that the nomogram has good predictive ability.
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28 The results for the validation cohort also show that the model is stable. This model
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30 can therefore help clinicians to quickly and easily determine the prognosis of
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32 individual patients and provide guidance in their clinical decision-making. However,
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34 the stability of the model needs further verification.
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43 Inevitably, our research had some limitations. First, the established model is not
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45 comprehensive enough, because the SEER database does not include all prognostic
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47 factors for UTUC. Second, the data available on the treatment status are not
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49 sufficiently detailed to distinguish the impact of various treatment plans. Finally, the
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51 model requires prospective studies to confirm its reliability.
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55 **5. Conclusions**

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

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22 **Contributorship statement:** JL, CZL, and XL designed the study; QH, FFZ, and
23
24 XJF collected and analyzed the data; CZL and XL drafted the initial manuscript;
25
26 DDH, FSX, and SZ reviewed and edited the article; All authors read and approved the
27
28 final manuscript.
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32
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34
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36
37

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39

40
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43 consent was unnecessary because the SEER research data are anonymous and
44
45 publicly available.
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48 **Patient consent for publication:** Not required.
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51 **Data availability statement:** The datasets generated and analyzed during the current
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53 study are available from the corresponding author on reasonable request.
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57 **Licence statement:** Other than as permitted in any relevant BMJ Author's Self
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59 Archiving Policies, I confirm this Work has not been accepted for publication
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4 elsewhere, is not being considered for publication elsewhere and does not duplicate
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6 material already published. I confirm all authors consent to publication of this Work
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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)

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

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5	Laterality			0.896			0.635
6	Left	26.117	31.350	33.726	24.117	30.669	35.750
7		(25.828-26.405)	(31.034-31.667)	(33.391-34.062)	(23.836-24.399)	(30.353-30.986)	(35.394-36.106)
8	Right	26.973	30.190	32.640	21.157	28.446	36.696
9		(26.647-27.298)	(29.846-30.535)	(32.274-33.006)	(20.857-21.457)	(28.096-28.797)	(36.283-37.108)
10							
11	Surgery			0.029			0.132
12	Yes	26.232	30.613	33.048	22.666	29.620	36.174
13		(26.016-26.447)	(30.380-30.846)	(32.800-33.296)	(22.460-22.872)	(29.384-29.856)	(35.903-36.445)
14	NO/Unknown	58.333	-	-	41.667	-	-
15		(54.877-61.790)			(38.639-44.695)		
16	Radiotherapy			<0.001			0.940
17	Yes	42.957	47.953	49.418	26.414	32.064	34.468
18		(42.073-43.841)	(47.041-48.865)	(48.485-50.351)	(25.633-27.196)	(31.216-32.911)	(33.584-35.351)
19	NO/Unknown	25.142	29.398	31.898	22.510	29.506	36.371
20		(24.922-25.363)	(29.159-29.637)	(31.643-32.154)	(22.297-22.723)	(29.261-29.750)	(36.087-36.654)
21	Chemotherapy			<0.001			0.007
22	Yes	35.840	41.411	44.178	20.103	26.626	31.696
23		(35.412-36.268)	(40.954-41.868)	(43.698-44.658)	(19.747-20.459)	(26.209-27.042)	(31.233-32.159)
24	NO/Unknown	22.389	26.245	28.493	24.052	31.128	38.226
25		(22.145-22.633)	(25.980-26.510)	(28.210-28.776)	(23.800-24.303)	(30.844-31.413)	(37.896-38.556)
26	Distant metastasis			<0.001			0.905
27	No	22.843	27.444	29.995	22.251	29.517	36.603
28		(22.627-23.059)	(27.206-27.682)	(29.740-30.251)	(22.036-22.465)	(29.270-29.765)	(36.316-36.891)
29	Yes	62.766	64.400	65.218	28.317	31.513	32.330
30		(61.998-63.533)	(63.634-65.167)	(64.451-65.984)	(27.603-29.032)	(30.767-32.258)	(31.577-33.083)
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5	LNE			0.002			0.699
6		29.182	34.316	36.877	21.861	29.193	36.619
7	1-3	(28.887-29.478)	(33.998-34.633)	(36.544-37.210)	(21.592-22.130)	(28.884-29.501)	(36.264-36.974)
8		22.696	26.540	28.034	26.331	30.175	35.705
9	4-7	(22.224-23.168)	(26.019-27.061)	(27.481-28.588)	(25.828-26.835)	(29.629-30.720)	(35.077-36.333)
10		23.311	26.017	28.677	22.268	30.242	34.775
11	≥8	(22.893-23.728)	(25.572-26.462)	(28.189-29.165)	(21.859-22.678)	(29.759-30.725)	(34.235-35.315)
12							
13	LNP			<0.001			0.009
14		16.502	21.003	23.860	18.979	27.239	35.417
15	No	(16.273-16.731)	(20.741-21.264)	(23.571-24.148)	(18.738-19.221)	(26.948-27.531)	(35.069-35.765)
16		44.145	48.231	49.950	29.565	34.071	37.613
17	Yes	(43.743-44.546)	(47.817-48.645)	(49.523-50.376)	(29.196-29.934)	(33.676-34.465)	(37.190-38.037)
18							
19	LNR			<0.001			<0.001
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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								

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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

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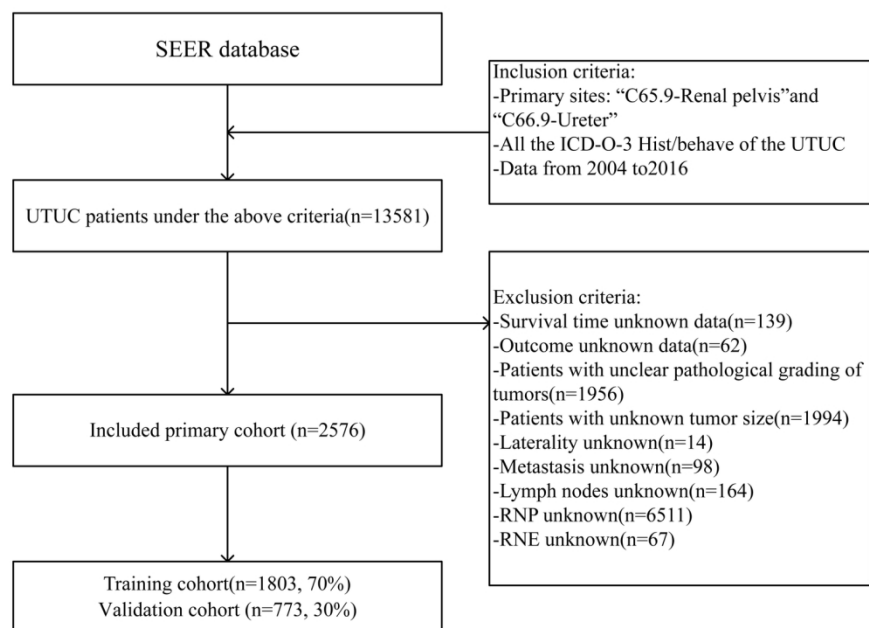
Figure legends

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.

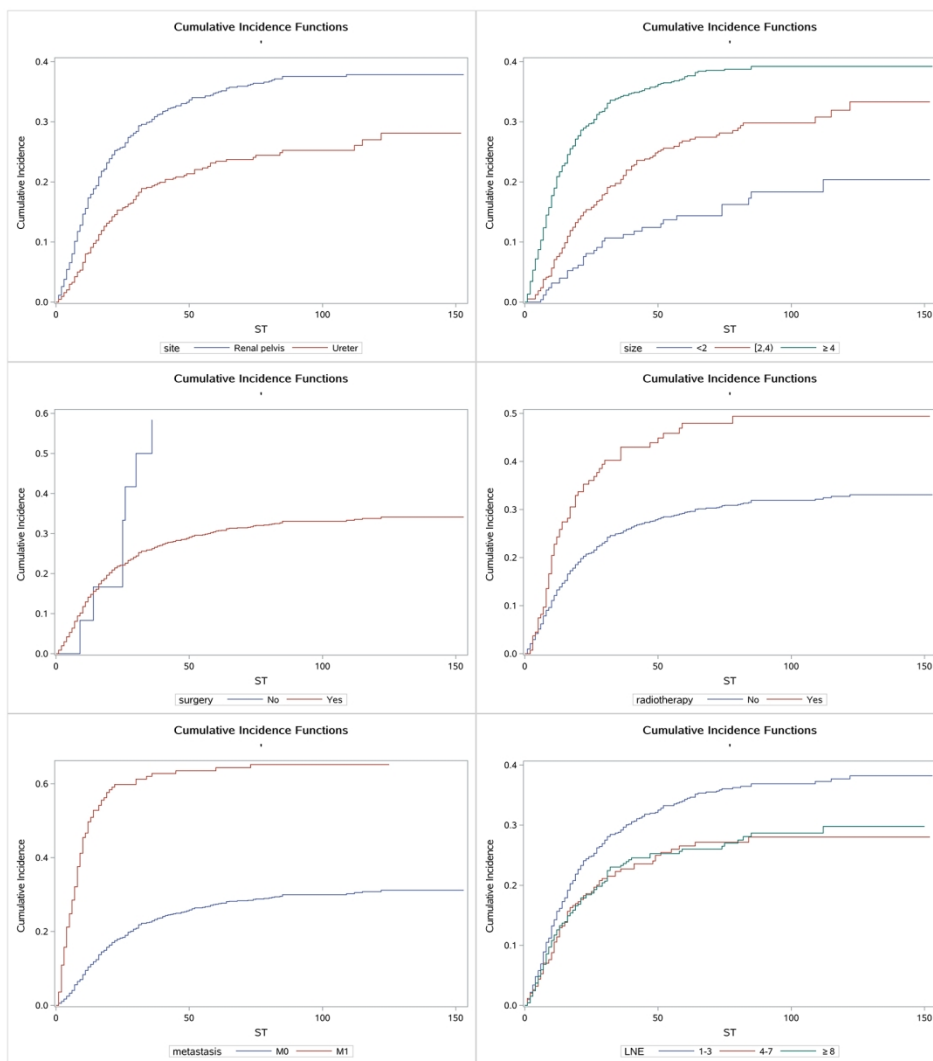
Figure 3. Nomogram based on the competing risk analysis to predict cancer-specific death probabilities at 3, 5, and 8 years for UTUC patients.

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.

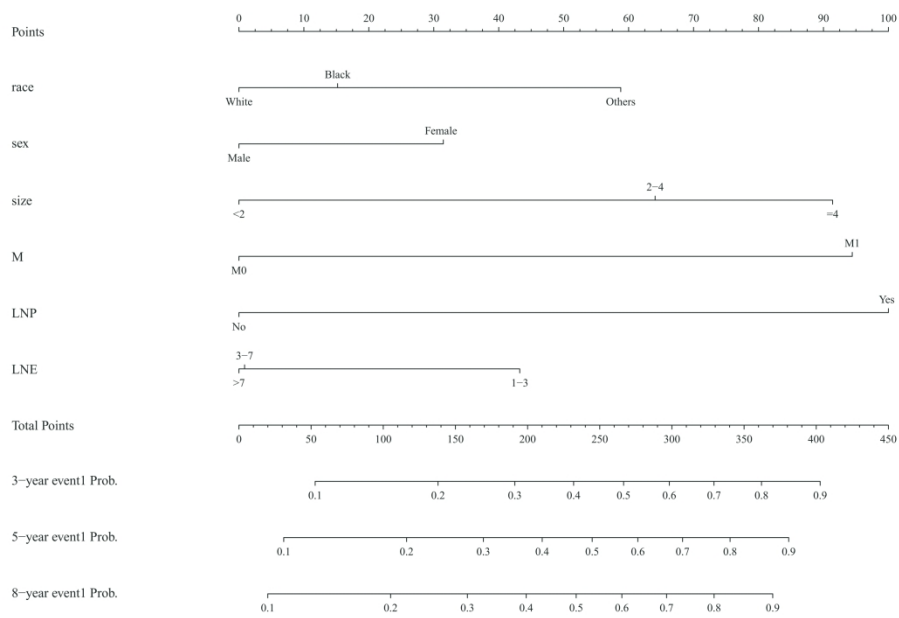
74x78mm (600 x 600 DPI)



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.

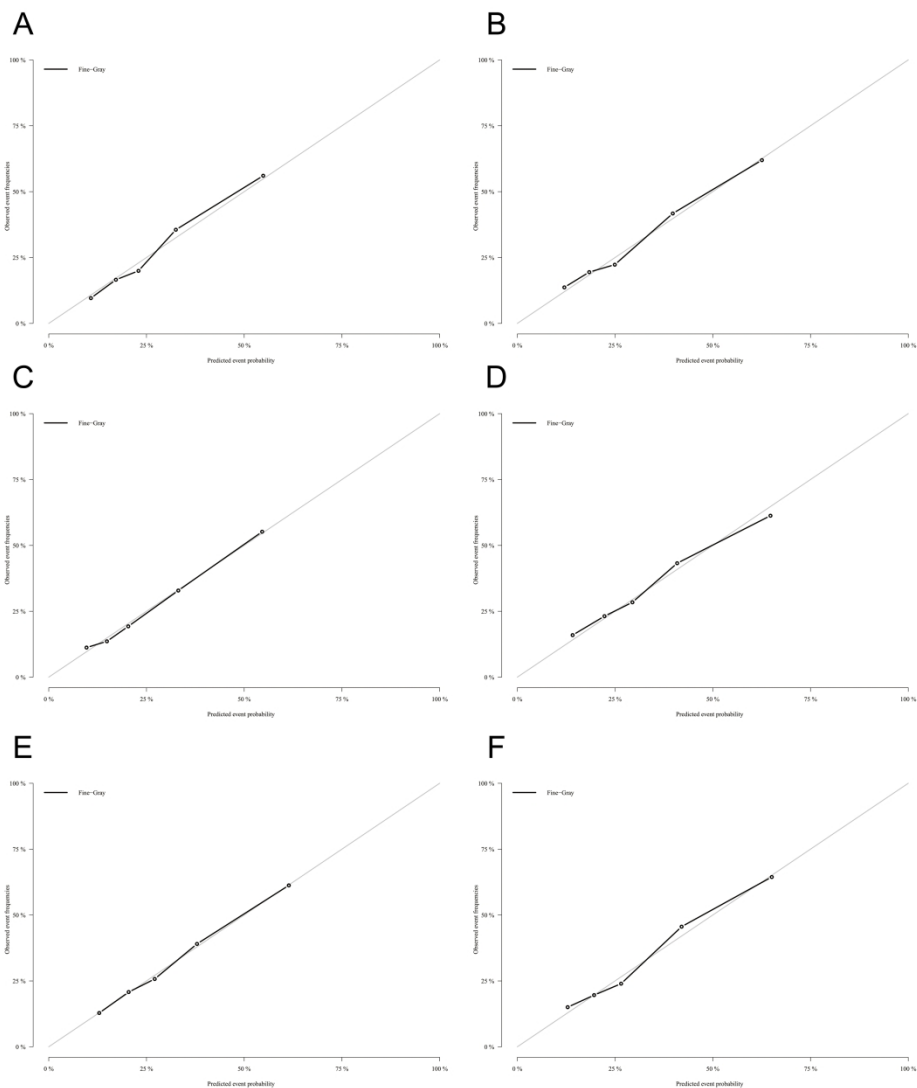
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Nomogram based on the competing risk analysis to predict cancer-specific death probabilities at 3, 5, and 8 years for UTUC patients.

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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

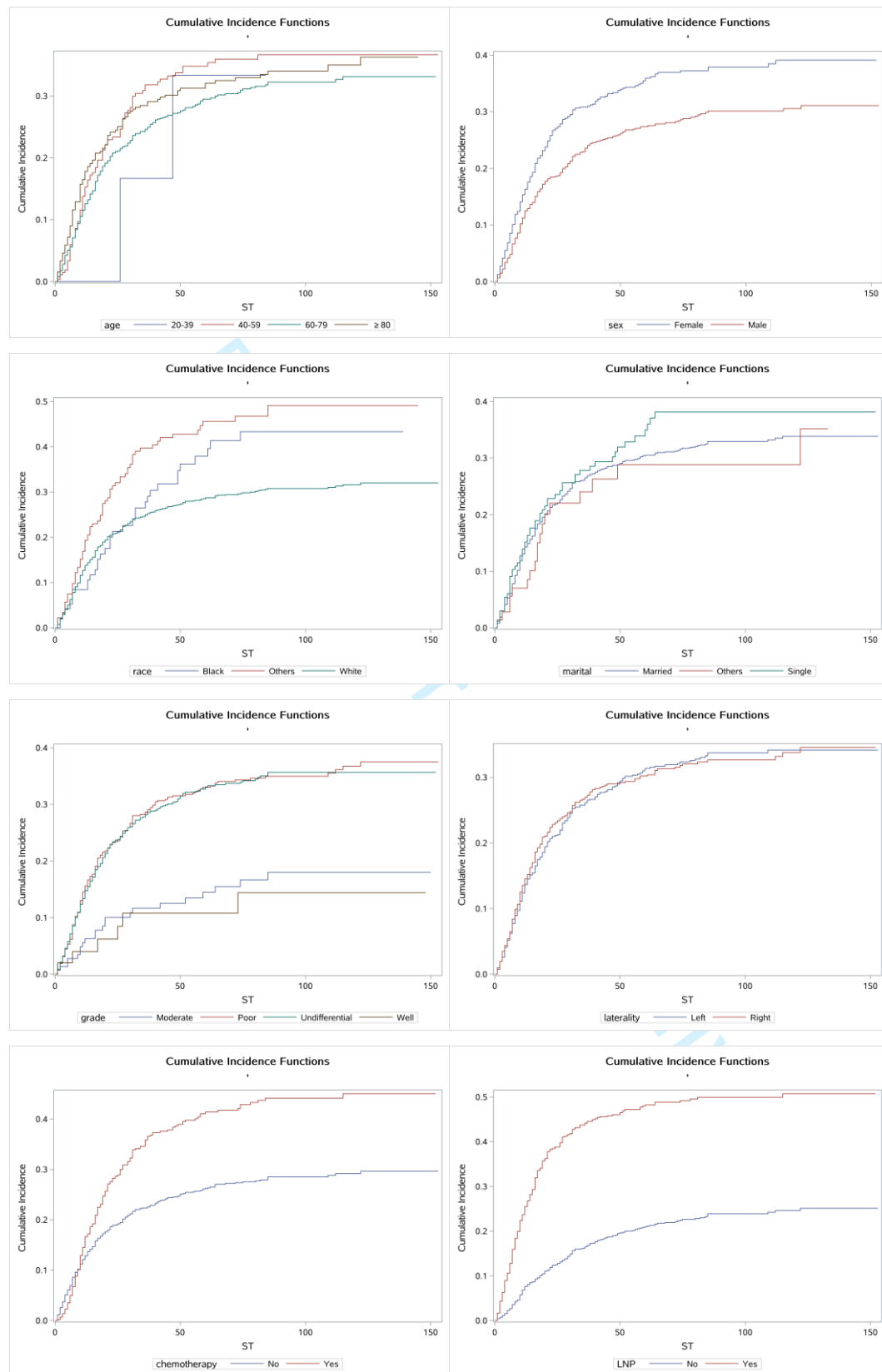
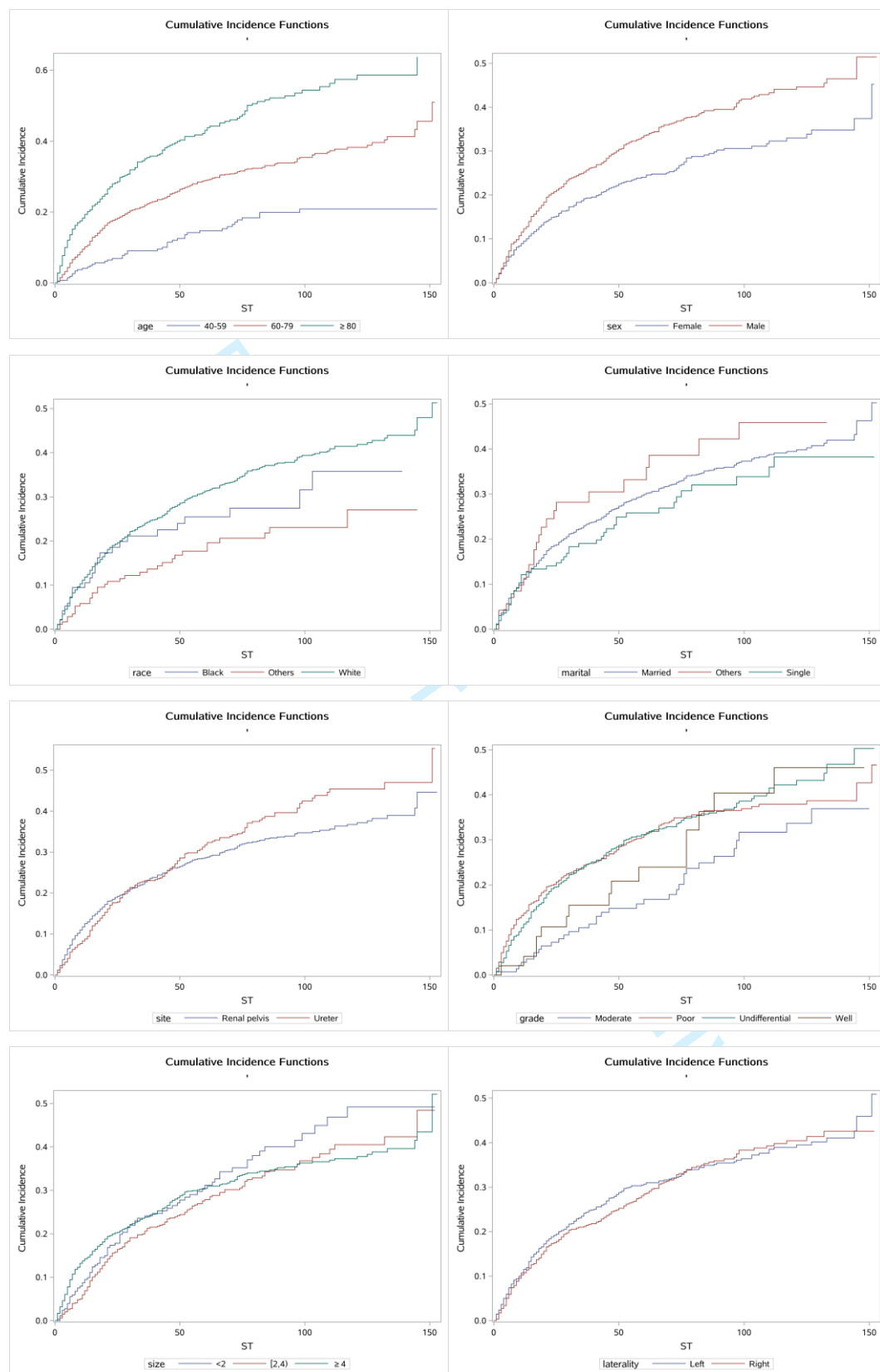


Figure 1. The CIF curves of UTUC cause-specific death. LNP: lymph nodes positive.

Figure 2



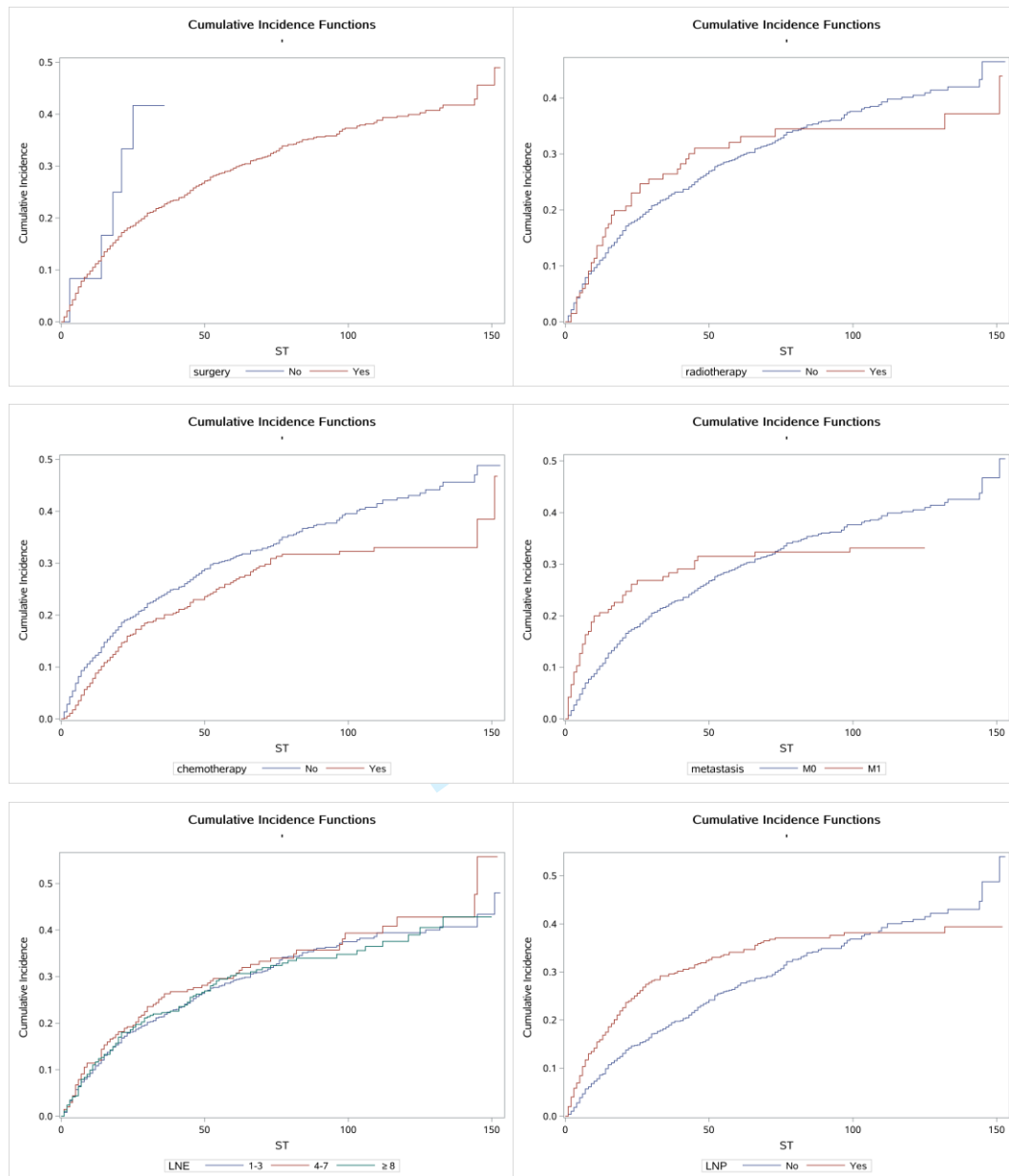


Figure 2. The CIF curves of death due to other causes of UTUC patients. LNE: lymph nodes examined; LNP: lymph nodes positive.

BMJ Open

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

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4 **A competing-risks nomogram for predicting cancer-specific death in**
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6 **upper-tract urothelial carcinoma: a population-based analysis**
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13 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

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4 factors associated with CSD were included in the nomogram. The 3, 5, and 8 years
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6 concordance indexes(C-indexes) were 0.714, 0.698, and 0.688 in the training cohort,
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8 respectively, and 0.693, 0.670, and 0.665 in the validation cohort.
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12 **Conclusions:** The competing-risks model showed that sex, tumor size, distant
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14 metastasis, surgery status, LNP and LNR were associated with CSD. The nomogram
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16 predicts the probability of CSD in UTUC patients at 3, 5, and 8 years, which can
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18 improve the ability of clinicians to predict the survival probabilities in individual
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20 patients.
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30 **Strengths and limitations of this study:**

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33 •The study established the first competing risk nomogram for predicting the 3-, 5-,
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35 and 8-year specific mortality probability for UTUC based on a large retrospective
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37 sample, which can improve the ability of clinicians to predict the survival
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39 probabilities in individual patients.
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44 •The established model is not comprehensive enough, because the SEER database
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46 does not include all prognostic factors for UTUC.
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51 •The data available on the treatment status are not sufficiently detailed to distinguish
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53 the impact of various treatment plans.
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57 •The model requires prospective studies to confirm its reliability.
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7 **Keywords:** competing risk model, upper-tract urothelial carcinoma(UTUC),
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10 nomogram, SEER, cancer-specific death
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13 **Abbreviations:** UTUC: upper-tract urothelial carcinoma; CSD: cancer-specific death;
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16 DOC: death due to other causes; SEER: Surveillance, Epidemiology, and End
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18 Results; LNE: lymph nodes examined; LNP: lymph nodes positive; K-M:
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20 Kaplan-Meier; CIF: cumulative incidence function; ICD-O-3: International
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22 Classification of Diseases for Oncology-3; LNR: lymph nodes ratio; C-index:
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24 concordance index; CS: cause-specific hazard function; SD: subdistribution
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26 proportional-hazards function
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36 **Introduction**

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39 Urothelial carcinomas are the fourth most common type of tumor,[1] and they can
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41 be located in the upper urinary tract or the lower. Upper-tract urothelial carcinoma
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43 (UTUC), which includes renal pelvis and ureter carcinoma, currently accounts for 5%
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45 of urothelial malignancies. [2] The annual incidence of UTUC is typically estimated
46
47 at 1 or 2 per 100,000 inhabitants in Western countries.[3] However, the increasing
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49 morbidity and mortality associated with UTUC[4, 5] are increasing the importance of
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51 this research.
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4 A study showed that UTUC has unique prognostic factors, which are different
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6 from bladder cancer and other urinary tract cancers.[6] Most studies analyzing the
7
8 prognostic factors for UTUC have adopted the Kaplan-Meier (K-M) method or Cox
9
10 regression methods.[7–9] These methods consider only a single end point when
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12 determining survival parameters. However, in addition to interest event, there are
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14 often competing events in clinical research. Competing events for cancer deaths refer
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16 to death from other causes not related to the primary cancer, such as other diseases,
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18 car collisions, and suicide. In traditional survival analysis, these events would be
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20 considered as censored, which would cause the cumulative incidence rate of cancer
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22 deaths to be overestimated. Applying standard survival analysis to competing-risks
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24 data leads to false and biased results.[10] While all-cause death as the study endpoint
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26 does not lead to competing risks bias, such an analysis could not reflect the influence
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28 of factors on the specific endpoint of cancer deaths. Therefore, the cumulative
29
30 incidence function (CIF) of UTUC cancer-specific death (CSD) needs to be calculated
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32 and prognostic factors for UTUC analyzed using the Fine-Gray subdistribution
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34 proportional-hazards model.[11]

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46 The purpose of our research was to identify the prognostic factors of UTUC
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48 based on competing risks model and used them to construct a nomogram to predict
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50 the survival rates of patients at the 3, 5, and 8 years. A nomogram is based on a
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52 prognostic model and graphically presents the predictive abilities of different
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54 prognostic factors as the lengths of line segments. This format makes it easy for
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4 clinicians to make rapid and comprehensive judgments and to predict the
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6 probability of CSD, which has great clinical significance. Some studies have
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8 constructed competing-risks nomograms for cancers such as sarcoma and prostate
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10 cancer,[12, 13] but research related to UTUC has been lacking.
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15 The current study was conducted to assess the effect of several factors in UTUC
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17 using a competing-risks method, and to construct a comprehensive nomogram that
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19 presents the impacts of these prognostic factors in order to guide clinical work.
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23 **Methods**

24 **Database and patients**

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27 The Surveillance, Epidemiology, and End Results (SEER) program has yielded a
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29 database of all cancer patients in 18 defined geographic regions of the United States
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31 collected by the National Cancer Institute. It is the largest cancer registry in the
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33 United States and includes information on approximately 28% of the United States
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35 population. Because part of the SEER research data is publicly available, no informed
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37 consent or institutional review board approval is required when analyzing the data.
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39 We additionally requested chemotherapy data for inclusion in our research and
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41 obtained a license for using SEER software.[14, 15]
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52 We selected UTUC patients from the latest edition of the SEER database that
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54 covers from 1975 to 2016. The primary sites were extracted using the SEER codes of
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56 “C65.9-Renal pelvis” and “C66.9-Ureter.” Patients between 2004 and 2015 were
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4 included in the study. We included all of the histological subtypes of UTUC,
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6 according to the ICD-O-3 (third revision of the International Classification of
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8 Diseases for Oncology). The following demographic indicators were selected: age at
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10 diagnosis, sex, race, and marital status. Primary site, histological grade, tumor size,
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12 laterality, distant metastasis, surgery status, radiotherapy status, chemotherapy status,
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14 number of lymph nodes examined (LNE), lymph nodes positive (LNP), and lymph
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16 nodes ratio (LNR; calculated as the number of LNP divided by LNE) were also
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18 included as pathological characteristics. The tumor size was categorized into three
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20 groups: <2 , $2-4$, and ≥ 4 cm.[1, 16] The study outcomes included CSD and death due
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22 to other causes (DOC). The survival time was reported in the available data in
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24 months.
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33 **Exclusion criteria**

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

51 **Statistical methods**

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57 We randomly divided the 2576 eligible patients into 2 groups using R software
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4 (version 3.5.3, The R Foundation for Statistical Computing, Vienna, Austria;
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6 <http://www.r-project.org>): 70% (n=1803) in the training cohort and 30% (n=773) in
7
8 the validation cohort. We first described the basic composition of each factor in the
9
10 two patient cohorts using R software. The age, LNE, LNP and LNR were expressed
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12 as median and interquartile-range values, while categorical variables were represented
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14 as percentages. We evaluated differences in patient characteristics between two
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16 groups using the Student's t-test and Chi-square test.
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23 We used the cumulative incidence function (CIF) to describe the probability of
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25 each event, and also plotted the corresponding CIF curves. And then we do univariate
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27 analysis by using Gray's test to estimate the difference in the CIF between groups.
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29 The significant variables ($P < 0.05$) were put into multivariable regression model. The
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31 Fine-Gray subdistribution proportional-hazards model was used for the multivariate
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33 analysis and compared the results with using cancer-specific hazards model. Applying
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35 the standard Cox regression method ignores the presence of competing risks and
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37 hence overestimates the actual incidence of beneficial events, and so may lead to
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39 inappropriate risk stratification.[17] Several studies have confirmed that different
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41 approaches can be used in competing-risks settings for multivariate survival analysis,
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43 but subdistribution proportional-hazards model have been found to be the best
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45 predictors of survival probability.[18-20]
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55 Finally, the results of Fine-Gray subdistribution proportional-hazards model were
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57 used to construct a nomogram of the 3, 5, and 8 years CSD rates, which was tested
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4 using the validation cohort. We used the concordance index (C-index) and calibration
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6 plots to evaluate the differentiation ability and consistency of the established model.
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10 All statistical tests were conducted using R software (version 3.5.3). Probability
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12 values of $P < 0.05$ were considered statistically significant, and all tests were
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14 two-sided. The SEER database can be accessed free of charge, and this study was
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16 exempted from obtaining informed consent.
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20 21 **Patients and public involvement**

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

40 41 42 **Patient characteristics**

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46 The composition of each variable for the 2576 patients in the training and
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48 validation cohorts is presented in Table 1. This table indicates that the median age
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50 was 71 years in the training and validation cohorts, respectively. The majority of
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52 patients were male (60.6% and 57.4%), white (86.2% and 82.5%), and married
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54 (86.8% and 87.6%). The main UTUC sites were in the renal pelvis (63.9% and 62.7%,
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4 respectively, in the training and validation cohorts), with the rest in the ureter.
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6 Majority of patients were in the undifferentiated stage (58.1% and 55.6%), and most
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8 of the tumors in both cohorts were larger than 4 cm. Most patients in both cohorts had
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10 received surgery, whereas a few patients had received radiotherapy or chemotherapy.
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12 Only about 9% of patients had distant metastasis. Baseline characteristics were
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14 basically similar in the training and validation cohorts.
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Table 1

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23 **Univariate analysis**

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

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53 **Multivariate analysis**

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55 Our comparison of the proportional subdistribution hazards model with
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4 cancer-specific hazards model yielded the results presented in Table 3. The
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6 cancer-specific hazards model showed that sex, tumor size, distant metastasis, LNP
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8 and LNR were prognostic factors for UTUC ($P < 0.001$). We then constructed the
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10 Fine-Gray subdistribution proportional-hazards model, which indicated that sex
11
12 (hazard ratio [HR]=1.481 for female, 95% confidence interval [CI]=1.243–1.766),
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14 tumor size (HR=1.563 for 2–4 cm, 95% CI=1.098–2.226; HR=2.204 for ≥ 4 cm, 95%
15
16 CI=1.575–3.086), surgery status (HR=2.915 for no/unknown surgery,
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18 95% CI=1.289–3.738), distant metastasis (HR=2.419 for distant, 95%
19
20 CI=1.847–3.169), LNP (HR=1.064, 95% CI=1.022–1.107), and LNR (HR=1.871, 95%
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22 CI=1.434–2.442) were prognostic factors affecting UTUC, as presented in Table 3.
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31 **Table 3**

32 33 34 35 36 37 **Construction and verification of the nomogram**

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41 Figure 3 shows the nomogram we constructed according to the results of the
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43 Fine-Gray subdistribution proportional-hazards model for predicting the CSD
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45 probabilities at 3, 5, and 8 years. The figure shows that LNP had the greatest impact
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47 on the probability of CSD, followed by distant metastasis, tumor size, LNR, surgery,
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49 and sex.
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55 We used the validation cohort to verify the nomogram after establishing it. The 3,
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57 5, and 8 years C-indexes were 0.714, 0.698, and 0.688 for the training cohort,
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4 respectively, and 0.693, 0.670, and 0.665 for the validation cohort. All of these values
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6 exceeded 0.6, which indicated that the model had good discrimination ability. We
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8 then tested the prediction accuracy of the model. As shown in Figure 4, the 3, 5, and 8
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10 years calibration plots for both cohorts were very close to the standard straight line,
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13 demonstrating that the model was well calibrated.
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18  Figures 3, 4
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24 **Discussion**

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28 The increasing incidence of UTUC[21] makes it necessary to further explore the
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30 prognostic factors for UTUC. The present study used a competing-risks model to
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32 more accurately explore the prognostic factors for UTUC, and used these factors to
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34 construct a nomogram to provide clinicians with direct guidance when they are
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36 making relevant predictions.
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42 The application of study criteria resulted in the inclusion in 2576 patients from
43
44 the SEER database, and 1542 of these patients died during the follow-up, although
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46 only 750 of the deaths were related to UTUC. This means that the number of DOC
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48 patients was almost the same as that for CSD. In this situation, if the traditional K-M
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50 or Cox survival analysis had been adopted, the DOC patients will be considered as
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52 censored. This would lead to the overestimation of the cumulative incidence rate of
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54 CSD and hence not truly reflect the prognosis.[22, 23] We overcame this shortcoming
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4 by using competing risks model, which can properly address the situation where the
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6 available data are related to multiple potential outcomes.[24] This method was first
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9 proposed by Fine and Gray, and has also been applied in some previous
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11 studies.[17,25–26] In the presence of competing risks, there are usually two models,
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13 one is cause-specific hazards function (CS), the other is subdistribution
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15 proportional-hazards function (SD), and the latter is also called Fine-Gray model. We
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17 analyzed and compared the two models in this study. Because CS is suitable for
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19 answering etiological questions, and SD is suitable for establishing clinical prediction
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21 models and risk scores. Therefore, we used the CIF and the subdistribution
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23 proportional-hazards model to explore the impact of various factors on the prognosis
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25 of CSD.
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33 The univariate analysis results showed that age, sex, race, primary site,
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35 histological grade, tumor size, surgery status, radiotherapy status, chemotherapy
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37 status, distant metastasis, LNE, LNP, and LNR were influencing factors for CSD,
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39 while age, sex, histological grade, chemotherapy status, and LNR were influencing
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41 factors for DOC. The cause-specific hazards model results showed that age, sex,
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43 histological grade, tumor size, distant metastasis, LNP, and LNR were prognostic
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45 factors for CSD. The subdistribution proportional-hazards model showed that sex,
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47 tumor size, surgery, distant metastasis, LNP, and LNR are independent prognostic
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49 factors for CSD.
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54 factors for CSD.
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57 Age is a prognostic factor for most cancers, and so is for UTUC.[27, 28] Our CS
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4 model showed that age was a predictor of CSD, however, it is not statistically
5
6 significant in the SD model. This may be because of the effect of age on DOC higher
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8 than the CSD, namely elderly patients are more likely to death of other causes, which
9
10 competitively leads to the fact that the incidence of CSD does not increase
11
12 significantly with age. Previous studies may have ignored competing events, and sex
13
14 and race have always been controversial prognostic factors. One study showed that
15
16 age and race are preoperative prognostic factors for UTUC patients.[29] In contrast,
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18 another study found no statistically significant differences in survival between males
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20 and females.[30] The competing-risks model in our study showed that sex was a risk
21
22 factor for UTUC. However, since most of the patients included in the SEER database
23
24 are white, the results regarding race need to be further validated.
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33 Tumor size has always been a prognostic factor. One study found 5-year
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35 recurrence-free survival rates for patients with tumor sizes <3 cm and ≥ 3 cm of 46.9%
36
37 and 25.8%, respectively.[31] The univariate and multivariate analyses performed in
38
39 the present study indicated that tumor size was an influencing factor for CSD, with
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41 the prognosis being worse for tumors larger than 2 cm. In terms of treatment methods,
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43 surgery status was a significant prognostic factor, which was consistent with the
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45 findings of Yuval et al.[32] Thus, it should be noted that the gold standard treatment
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47 for UTUC is still surgery. However, radiotherapy status, and chemotherapy status
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49 were not influencing factors for CSD in both competing risks models. This conflicts
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51 with some previous findings,[33–35] suggesting that traditional Cox regression
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4 analysis overestimates the effects of radiotherapy, and chemotherapy. Of course, the
5
6 relative lack of information on the radiotherapy status and chemotherapy status in the
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8 SEER database may also lead to inaccurate results, and so further exploration of these
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10 indicators is needed.
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15 Some indicators related to lymph nodes (e.g., distant lymph node metastasis,
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17 LNP, and LNE) have been found to be important clinical information for the
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19 prognosis of cancer, but whether they are independent prognostic factors for UTUC
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21 has not been determined. One study found that lymph node metastases were
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23 significantly associated with reduced disease-specific survival in univariate
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25 analysis.[36] Our research also found that distant metastasis is an important
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27 prognostic factor for CSD, in both the univariate and multivariate analyses.
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34 It is worth noting that very few studies have investigated LNP, LNE, and LNR.
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36 Our study is the first to use the SEER database to analyze the prognostic impact of
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38 these indicators on UTUC, and the results may be more accurate than those of studies
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40 involving small samples. LNR is an emerging indicator that has been regarded as a
41
42 prognostic factor in rectal cancer and breast cancer.[37, 38] Our results suggested that
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44 LNR was also an important prognostic indicators for UTUC. We found that LNE was
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46 an influencing factor for UTUC in the univariate analysis but not in the multivariate
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48 analysis. Moreover, both LNR and LNP entered the subdistribution proportional
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50 hazards model, which showed that after adjusting for the effects of LNR and LNP,
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52 LNE was no longer an independent prognostic indicator. LNP was a prognostic factor
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4 in all of the analyses, indicating that it greatly influences the prognosis of UTUC.
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7 We utilized the results from the above-mentioned subdistribution
8 proportional-hazards model to construct a nomogram that graphically presents the
9 degrees of influence of various prognostic factors. This nomogram also integrates
10 various indicators to predict the 3, 5, and 8 years probabilities of CSD. The predictive
11 function of nomogram has been used for different types of cancer, and has even been
12 proposed as a new standard. For example, in order to calculate the death probability of
13 a specific cause of death of a UTUC patient, find the patient's sex (Male or Female)
14 on the sex row, draw a vertical line on the dot row, and get the sex score value.
15 Repeat the above steps for tumor size, M stage, surgery, LNP and LNR. Add the point
16 values of each variable, find the total point on the total point axis, and draw a straight
17 downward line to get the probability of death of a UTUC patient due to a specific
18 cause. For example, a female (30 points), with a tumor size of 1.5cm (0 points), M1
19 (68 points), surgery status is yes (0 points) LNP equal to 5 (15 points), and LNR equal
20 to 0.8 (45 points), the total score is 158 points, which correspond to 3, 5, and 8 years
21 of specific cause of death probability of 58%, 64% and 69%, respectively.
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47 The C-indexes for the nomogram all exceeded 0.6, demonstrating that the model
48 provides a good fit to the available data. The prediction calibration curves in Figure 4
49 are very close to the standard curve, which indicates that the nomogram has good
50 predictive ability. The results for the validation cohort also show that the model is
51 stable. This model can therefore help clinicians to quickly and easily determine the
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4 prognosis of individual patients and provide guidance in their clinical
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6 decision-making. However, the stability of the model needs further verification.
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10 Inevitably, our research had some limitations. First, the established model is not
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12 comprehensive enough, because the SEER database does not include all prognostic
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14 factors for UTUC. Second, the data available on the treatment status are not
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16 sufficiently detailed to distinguish the impact of various treatment plans. Finally, the
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18 model requires prospective studies to confirm its reliability.
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23 **5. Conclusions**

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

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50 **Contributorship statement:** JL, CZL, and SZ designed the study; QH, DDH, and
51
52
53 FSX collected and analyzed the data; CZL and XL drafted the initial manuscript;
54
55
56 FFZ, and XJF reviewed and edited the article; All authors read and approved the
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4 final manuscript.
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9
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11
12

13 **Competing interests:** The authors declare that they have no competing interests.
14
15

16 **Availability of data and materials:** Ethical approval was waived, and informed
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18 consent was unnecessary because the SEER research data are anonymous and
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20 publicly available.
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25 **Patient consent for publication:** Not required.
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29 **Data availability statement:** The datasets generated and analyzed during the current
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31 study are available from the corresponding author on reasonable request.
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35 **Ethics approval:** The data analyses and use of the SEER database in our manuscript
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37 are in accordance with the DUA and do not require institutional review board
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39 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	<i>p</i>
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)	

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4	Grade, n (%)			0.481
5				
6	Grade I	47 (2.6)	16 (2.1)	
7				
8	Grade II	149 (8.3)	69 (8.9)	
9				
10	Grade III	559 (31.0)	258 (33.4)	
11				
12	Grade IV	1048 (58.1)	430 (55.6)	
13				
14				
15	Size, n (%)			0.188
16				
17	[2,4)	559 (31.0)	268 (34.7)	
18				
19	<2	262 (14.5)	106 (13.7)	
20				
21	>=4	982 (54.5)	399 (51.6)	
22				
23				
24				
25	Laterality, n (%)			0.551
26				
27	Left	995 (55.2)	416 (53.8)	
28				
29	Right	808 (44.8)	357 (46.2)	
30				
31				
32	Surgery, n (%)			0.203
33				
34	NO/Unknown	9 (0.5)	8 (1.0)	
35				
36	Yes	1794 (99.5)	765 (99.0)	
37				
38				
39	Radiotherapy, n (%)			0.931
40				
41	NO/Unknown	1676 (93.0)	720 (93.1)	
42				
43	Yes	127 (7.0)	53 (6.9)	
44				
45				
46	Chemotherapy, n (%)			0.938
47				
48	NO/Unknown	1243 (68.9)	531 (68.7)	
49				
50	Yes	560 (31.1)	242 (31.3)	
51				
52				
53	Distant metastasis, n (%)			0.053
54				
55	M0	1652 (91.6)	689 (89.1)	
56				
57				
58				
59				
60				

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.

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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)

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5	Size				<0.001				0.727
6									
7	<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)		
8									
9	[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)		
10									
11	≥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)		
12									
13									
14	Laterality				0.944				0.393
15									
16	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)		
17									
18	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)		
19									
20									
21	Surgery				0.001				0.980
22									
23	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)		
24									
25	NO/Unknown	77.778 (76.910-78.646)	—	—	22.222 (21.522-22.923)	—	—		
26									
27									
28	Radiotherapy				<0.001				0.998
29									
30	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)		
31									
32	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)		
33									
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35	Chemotherapy				<0.001				0.003
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5	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)		
6									
7	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)		
8									
9									
10	Distant metastasis				<0.001				0.641
11									
12	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)		
13									
14	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)		
15									
16									
17	LNE	—	—	—	<0.001	—	—	—	0.941
18									
19	LNP	—	—	—	<0.001	—	—	—	0.448
20									
21	LNR	—	—	—	<0.001	—	—	—	<0.001
22									
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27	Abbreviations: CI, confidence interval; LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.								
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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	<i>P</i>	Coefficient	csHR	95%CI	<i>P</i>
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.

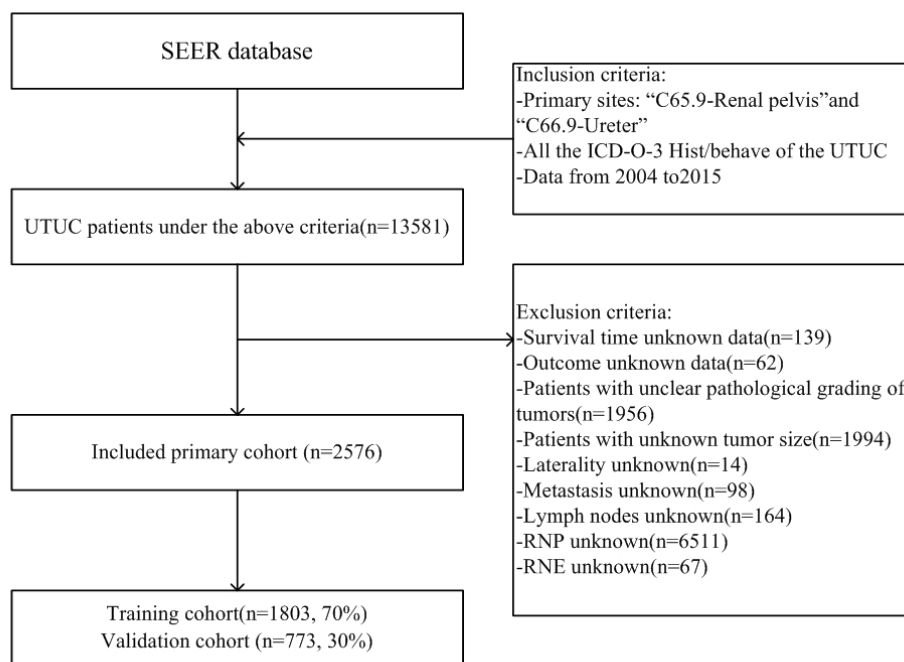


Figure 1. Data selection flowchart.

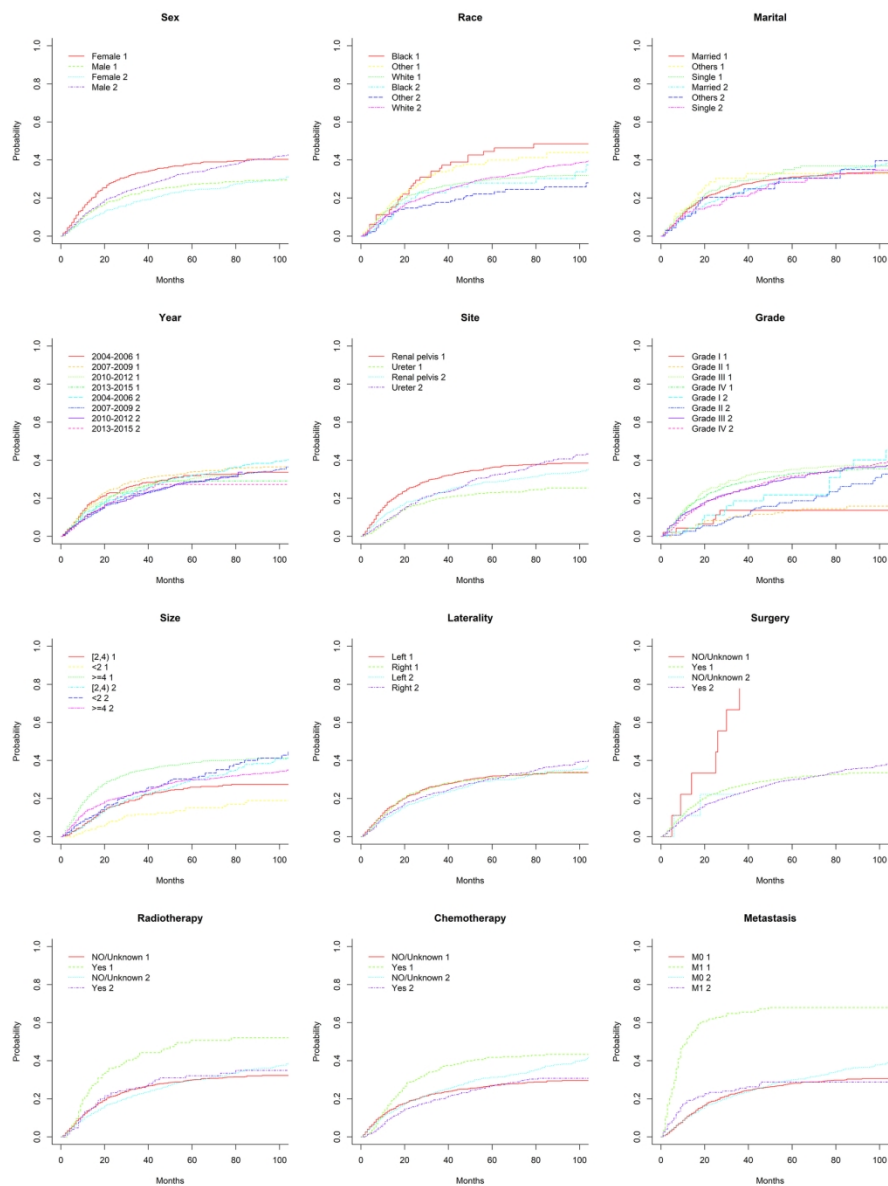


Figure 2. The CIF curves of UTUC cancer-specific death (CSD). Race, primary site, tumor size, surgery status, radiotherapy status, distant metastasis, LNE, and LNP were significantly related to the patients of CSD. LNE: lymph nodes examined; LNP: lymph nodes positive.

149x199mm (300 x 300 DPI)

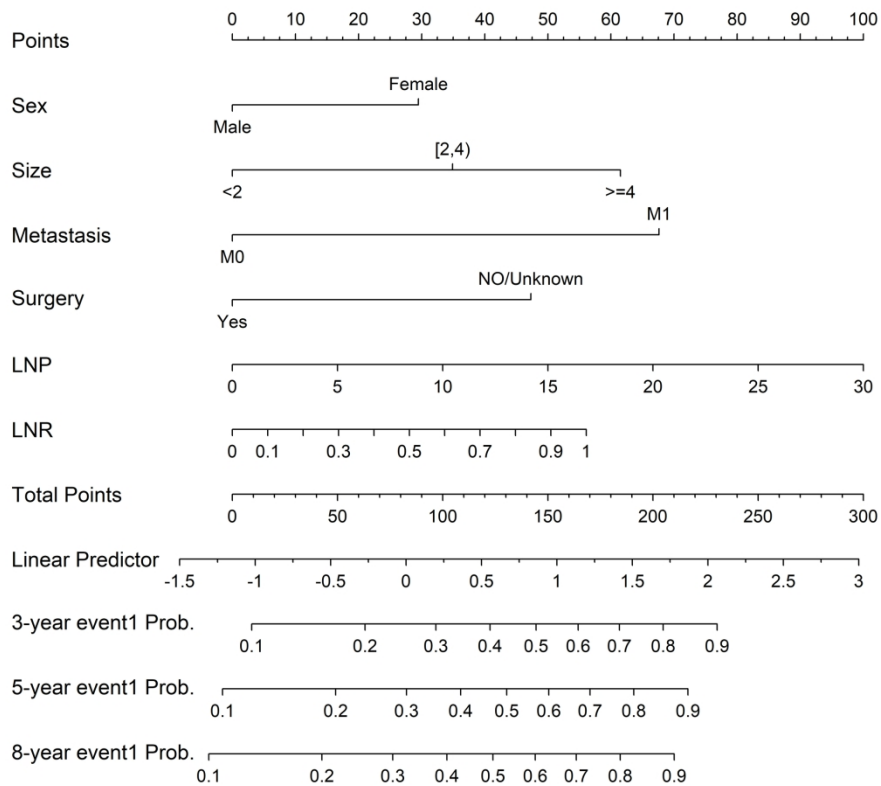


Figure 3. Nomogram based on the competing risk analysis to predict cancer-specific death probabilities at 3, 5, and 8 years for UTUC patients. LNE: lymph nodes examined; LNP: lymph nodes positive.

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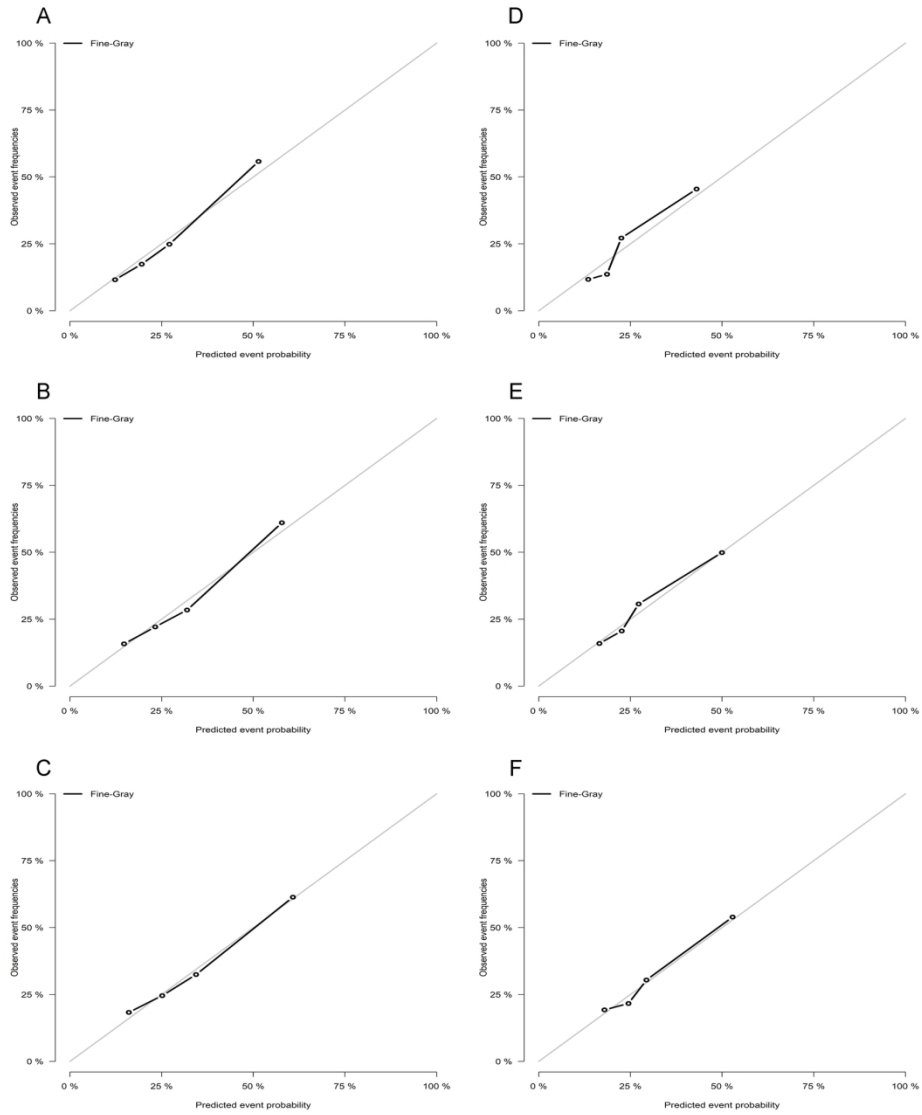


Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years calibration plots of the training (A, B, C) and validation (D, E, F) cohort.

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, if applicable.		
	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 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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BMJ Open

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

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Secondary Subject Heading:	Public health
Keywords:	EPIDEMIOLOGY, UROLOGY, Urological tumours < UROLOGY

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4 **A competing-risks nomogram for predicting cancer-specific death in**
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6 **upper-tract urothelial carcinoma: a population-based analysis**
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9 Running Head : Nomogram for UTUC cancer-specific death
10

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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.

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4 **Conclusions:** The competing-risks model showed that sex, tumor size, distant
5 metastasis, surgery status, LNP and LNR were associated with CSD. The nomogram
6 predicts the probability of CSD in UTUC patients at 3, 5, and 8 years, which can
7 improve the ability of clinicians to predict the survival probabilities in individual
8 patients.
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17 **Strengths and limitations of this study:**
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20 •The study established the first competing risk nomogram for predicting the 3-, 5-,
21 and 8-year specific mortality probability for UTUC based on a large retrospective
22 sample, which can improve the ability of clinicians to predict the survival
23 probabilities in individual patients.
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25 •The established model is not comprehensive enough, because the SEER database
26 does not include all prognostic factors for UTUC.
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28 •The data available on the treatment status are not sufficiently detailed to distinguish
29 the impact of various treatment plans.
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31 •The model requires prospective studies to confirm its reliability.
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43 **Keywords:** competing risk model, upper-tract urothelial carcinoma(UTUC),
44 nomogram, SEER, cancer-specific death
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48 **Abbreviations:** UTUC: upper-tract urothelial carcinoma; CSD: cancer-specific death;
49 DOC: death due to other causes; SEER: Surveillance, Epidemiology, and End
50 Results; LNE: lymph nodes examined; LNP: lymph nodes positive; K-M:
51 Kaplan-Meier; CIF: cumulative incidence function; ICD-O-3: International
52 Classification of Diseases for Oncology-3; LNR: lymph nodes ratio; C-index:
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4 concordance index; CS: cause-specific hazards model; SD: proportional
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6 subdistribution hazards model
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9 **Introduction**

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11 Urothelial carcinomas are the fourth most common type of tumor,[1] and they can
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13 be located in the upper urinary tract or the lower. Upper-tract urothelial carcinoma
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15 (UTUC), which includes renal pelvis and ureter carcinoma, currently accounts for 5%
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17 of urothelial malignancies. [2] The annual incidence of UTUC is typically estimated
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19 at 1 or 2 per 100,000 inhabitants in Western countries.[3] However, the increasing
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21 morbidity and mortality associated with UTUC[4, 5] are increasing the importance of
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23 this research.
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30 A study showed that UTUC has unique prognostic factors, which are different
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32 from bladder cancer and other urinary tract cancers.[6] Most studies analyzing the
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34 prognostic factors for UTUC have adopted the Kaplan-Meier (K-M) method or Cox
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36 regression methods.[7–9] These methods only consider a single endpoint when
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38 determining survival parameters. However, in clinical research, in addition to events
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40 of interest, there are often competing events. Competing events for cancer deaths refer
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42 to death from other causes not related to the primary cancer, such as other diseases,
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44 car collisions, and suicide. In traditional survival analysis, these events will be
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46 considered as censored, which will make the cumulative incidence of cancer deaths
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48 overestimated. Applying standard survival analysis to competing-risks data leads to
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50 false and biased results.[10] Although the use of all-cause death as the study endpoint
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52 does not cause a competing risks bias, such an analysis cannot reflect the influence of
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4 factors on the specific endpoint of cancer death. Therefore, the cumulative incidence
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6 function (CIF) of UTUC cancer-specific death (CSD) needs to be calculated and
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8 prognostic factors for UTUC analyzed using the Fine-Gray proportional
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10 subdistribution hazards model.[11]
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14 A nomogram is based on a prognostic model and graphically presents the
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16 predictive abilities of different prognostic factors as the lengths of line segments.
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18 This format makes it easy for clinicians to make rapid and comprehensive
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20 judgments and to predict the probability of CSD, which has great clinical
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22 significance. Some studies have constructed competing-risks nomograms for
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24 cancers such as sarcoma and prostate cancer,[12, 13] but research related to UTUC
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26 has been lacking.
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33 The purpose of our research was to identify the prognostic factors of UTUC
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35 based on competing risks model and used them to construct a nomogram to predict
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37 the survival rates of patients at the 3, 5, and 8 years.
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40 **Methods**

41 **Database and patients**

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43 The Surveillance, Epidemiology, and End Results (SEER) program has yielded a
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45 database of all cancer patients in 18 defined geographic regions of the United States
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47 collected by the National Cancer Institute. It is the largest cancer registry in the
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49 United States and includes information on approximately 28% of the United States
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51 population. Because part of the SEER research data is publicly available, no informed
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53 consent or institutional review board approval is required when analyzing the data.
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4 We additionally requested chemotherapy data for inclusion in our research and
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6 obtained a license for using SEER software.[14, 15]
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9 We selected UTUC patients from the latest edition of the SEER database that
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11 covers from 1975 to 2016. The primary sites were extracted using the SEER codes of
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13 “C65.9-Renal pelvis” and “C66.9-Ureter.” Patients between 2004 and 2015 were
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15 included in the study. We included all of the histological subtypes of UTUC,
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17 according to the ICD-O-3 (third revision of the International Classification of
18
19 Diseases for Oncology).The following demographic indicators were selected: age at
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21 diagnosis, sex, race, and marital status. Primary site, histological grade, tumor size,
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23 laterality, distant metastasis, surgery status, radiotherapy status, chemotherapy status,
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25 number of lymph nodes examined (LNE), lymph nodes positive (LNP), and lymph
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27 nodes ratio (LNR; calculated as the number of LNP divided by LNE) were also
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29 included as pathological characteristics. The tumor size was categorized into three
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31 groups: <2 , $2-4$, and ≥ 4 cm.[1, 16] The study outcomes included CSD and death due
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33 to other causes (DOC). The survival time was reported in the available data in
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35 months.
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45 **Exclusion criteria**

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

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4 Finally, the results of Fine-Gray proportional subdistribution hazards model were
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6 used to construct a nomogram of the 3, 5, and 8 years CSD rates. We used the
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8 concordance index (C-index) and calibration plots to evaluate the differentiation
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10 ability and consistency of the established model in both training and validation
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12 cohorts.
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17 All statistical tests were conducted using R software (version 3.5.3). Probability
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19 values of $P < 0.05$ were considered statistically significant, and all tests were
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21 two-sided. The SEER database can be accessed free of charge, and this study was
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23 exempted from obtaining informed consent.
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26 27 **Patients and public involvement** 28 29

30 This research was done without patient involvement. Patients were not invited to
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32 comment on the study design and were not consulted to develop patient-relevant
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34 outcomes or interpret the results. Patients were not invited to contribute to the writing
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36 or editing of this document for readability or accuracy.
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40 **Results** 41 42

43 **Patient characteristics** 44 45

46 The composition of each variable for the 2576 patients in the training and
47
48 validation cohorts is presented in Table 1. This table indicates that the median age
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50 was 71 years in the training and validation cohorts, respectively. The majority of
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52 patients were male (60.6% and 57.4%), white (86.2% and 82.5%), and married
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54 (86.8% and 87.6%). The main UTUC sites were in the renal pelvis (63.9% and 62.7%,
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56 respectively, in the training and validation cohorts), with the rest in the ureter.
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4 Majority of patients were in the undifferentiated stage (58.1% and 55.6%), and most
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6 of the tumors in both cohorts were larger than 4 cm. Most patients in both cohorts had
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8 received surgery, whereas a few patients had received radiotherapy or chemotherapy.
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11 Only about 9% of patients had distant metastasis. The baseline characteristics of the
12
13 training cohorts and validation cohorts were basically similar.
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Table 1

18 19 **Univariate analysis**

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22 We calculated the 3, 5, and 8 years cumulative incidence rates of CSD and DOC.
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24 Year, laterality, and marital status were not related to either outcome ($P>0.05$), while
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26 age, sex, histological grade, chemotherapy status, and LNR were related to both
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28 outcomes ($P<0.05$). Race, primary site, tumor size, surgery status, radiotherapy status,
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30 distant metastasis, LNE, and LNP were significantly related to CSD. The
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32 corresponding CIF curves are shown in Figure 2. The cumulative incidence of CSD
33
34 and DOC are compared in Table 2.
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Figure 2, Table 2

41 42 43 44 45 **Multivariate analysis**

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

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4 hazards model to explore the impact of various factors on the prognosis of CSD.
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6 The univariate analysis results showed that age, sex, race, primary site,
7 histological grade, tumor size, surgery status, radiotherapy status, chemotherapy
8 status, distant metastasis, LNE, LNP, and LNR were influencing factors for CSD,
9 while age, sex, histological grade, chemotherapy status, and LNR were influencing
10 factors for DOC. The cause-specific hazards model results showed that age, sex,
11 histological grade, tumor size, distant metastasis, LNP, and LNR were prognostic
12 factors for CSD. The proportional subdistribution hazards model showed that sex,
13 tumor size, surgery, distant metastasis, LNP, and LNR are independent prognostic
14 factors for CSD.
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30 Age is generally considered to be a prognostic factor for most cancers, and so is
31 for UTUC.[27, 28] Our CS model showed that age was a predictor of CSD, however,
32 it was not statistically significant in the SD model. This may be because of the effect
33 of age on DOC is higher than the CSD, namely elderly patients are more likely to
34 death of other causes, which competitively leads to the fact that the incidence of CSD
35 does not increase significantly with age. Sex and race have always been controversial
36 prognostic factors. One study showed that race was a preoperative prognostic factors
37 for UTUC patients.[29] And another study found no statistically significant
38 differences in survival between males and females.[30] However, the competing-risks
39 model in our study showed that sex was a risk factor for UTUC, while race was not.
40 This may be because previous studies ignored the effect of competing risks. However,
41 since most of the patients included in the SEER database are white, the results
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4 regarding race need to be further validated.
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7 Tumor size is also generally considered to be related to cancer prognosis. One
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9 study found 5-year recurrence-free survival rates for UTUC patients with tumor sizes
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11 <3 cm and ≥ 3 cm of 46.9% and 25.8%, respectively.[31] The univariate and
12
13 multivariate analyses performed in the present study also indicated that tumor size
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15 was an influencing factor for CSD, with the prognosis being worse for tumors larger
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17 than 2 cm. In addition, our research also found that distant metastasis was an
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19 important risk factor for CSD. In terms of treatment methods, our study suggested that
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21 surgery status was a significant prognostic factor, which was consistent with the
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23 findings of Yuval et al.[32] In fact, surgery has long been considered the gold
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25 standard of UTUC treatment. However, radiotherapy status, and chemotherapy status
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27 were not influencing factors for CSD in both competing risks models. This conflicted
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29 with some previous findings,[33–35] suggesting that traditional Cox regression
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31 analysis overestimated the effects of radiotherapy and chemotherapy. Of course, the
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33 relative lack of information on the radiotherapy status and chemotherapy status in the
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35 SEER database may also lead to inaccurate results, and so further exploration of these
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37 indicators is needed.
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48 Some indicators related to lymph nodes (e.g., distant lymph node metastasis,
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50 LNP, and LNE) have been found to be important clinical information for the
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52 prognosis of cancer, but whether they are independent prognostic factors for UTUC
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54 has not been determined. One study found that lymph node metastases were
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56 significantly associated with reduced cancer-specific survival in univariate
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4 analysis.[36] It is worth noting that very few studies have investigated LNP, LNE, and
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6 LNR. Our study is the first to use the SEER database to analyze the prognostic impact
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8 of these indicators on UTUC, and the results may be more accurate than those of
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10 studies involving small samples. LNR is an emerging indicator that has been regarded
11
12 as a prognostic factor in rectal cancer and breast cancer.[37, 38] Our results also
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14 suggested that LNR was an important prognostic factor of UTUC. We found that LNE
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16 was an influencing factor for UTUC in the univariate analysis but not in the
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18 multivariate analysis. Moreover, both LNR and LNP entered the proportional
19
20 subdistribution hazards model, which showed that after adjusting for the effects of
21
22 LNR and LNP, LNE was no longer an independent prognostic indicator. LNP was a
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24 prognostic factor in all of the analyses, indicating that it greatly influences the
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26 prognosis of UTUC.
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35 We utilized the results from the above-mentioned proportional subdistribution
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37 hazards model to construct a nomogram that graphically presents the degrees of
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39 influence of various prognostic factors. This nomogram can be used to predict the 3,
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41 5, and 8 years probabilities of CSD in UTUC patients. The predictive function of
42
43 nomogram has been used for different types of cancer, and has even been proposed as
44
45 a new standard. The nomogram is easy to use. In order to calculate the CSD
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47 probability of a UTUC patient, find the patient's sex (Male or Female) on the sex row,
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49 draw a vertical line on the dot row, and get the sex score value. Repeat the above
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51 steps for tumor size, M stage, surgery, LNP and LNR. Add the score values of each
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53 variable, find the total point on the total point axis, and draw a straight downward line
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4 to get the 3, 5 and 8 years CSD probability of the UTUC patient. For example, a
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6 female (30 points), with a tumor size of 1.5cm (0 points), at M1 stage(68 points), had
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8 surgery performed (0 points), LNP equal to 5 (15 points), and LNR equal to 0.8 (45
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10 points), the total score is 158 points, which corresponds to 3, 5, and 8 years CSD
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12 probability of 58%, 64% and 69%, respectively.
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17 The C-indexes for the nomogram all exceeded 0.6, demonstrating that the model
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19 provided a good fit to the available data. The prediction calibration curves in Figure 4
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21 were very close to the standard curve, which indicated that the nomogram had good
22
23 predictive ability. The results for the validation cohort also showed that the model was
24
25 stable. This model can therefore help clinicians to quickly and easily determine the
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27 prognosis of individual patients and provide guidance in their clinical
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29 decision-making. However, the stability of the model needs further verification.
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35 Our study used the large sample size and high quality data from SEER database
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37 and competing risks model, which provided a guarantee for the accuracy of our study.
38
39 However, inevitably, our research had some limitations. First, the established model is
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41 not comprehensive enough, because the SEER database does not include all
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43 prognostic factors for UTUC. Second, the data available on the treatment status are
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45 not sufficiently detailed to distinguish the impact of various treatment plans. Third, as
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47 an retrospective study, our results may be affected by confounding bias to some
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49 extent, so the conclusion needs to be further verified in future prospective studies.
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51 Fourth, the cause of death in SEER is that according to the death certificate report,
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53 some deaths may have been misclassified, which may also bring information bias to
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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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Competing interests: The authors declare that they have no competing interests.

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.

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4 **Data availability statement:** The datasets generated and analyzed during the current
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6 study are available from the corresponding author on reasonable request.
7
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9 **Ethics statement:** The data analyses and use of the SEER database in our manuscript
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11 are in accordance with the DUA and do not require institutional review board
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13 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	<i>p</i>
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.

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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)	

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5	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)		
6	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)		
7	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)		
8									
9	Size				<0.001				0.733
10	<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)		
11	[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)		
12	≥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)		
13									
14	Laterality				0.944				0.393
15	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)		
16	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)		
17									
18	Surgery				0.001				0.980
19	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)		
20	NO/Unknown	77.778(76.910-78.646)	—	—	22.222(21.522-22.923)	—	—		
21									
22	Radiotherapy				<0.001				0.910
23	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)		
24	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)		
25									
26	Chemotherapy				<0.001				0.003
27	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)		
28	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)		
29									
30	Distant metastasis				<0.001				0.641
31	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)		
32	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)		
33									
34	LNE	—	—	—	<0.001	—	—	—	0.941
35	LNP	—	—	—	<0.001	—	—	—	0.448
36	LNR	—	—	—	<0.001	—	—	—	<0.001
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6 Abbreviations: CSD, cancer-specific death; DOC, death due to other causes; UTUC, upper-tract urothelial carcinoma; CI, confidence interval;
7 LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.
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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	<i>P</i>	Coefficient	csHR	95%CI	<i>P</i>
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								

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3									
4	Yes	Reference				Reference			
5	NO/Unknown	-0.219	0.803	0.594-1.087	0.160	-0.240	0.78	0.595-1.04	0.092
6							7	0	
7									
8	Chemotherapy								
9	Yes	Reference				Reference			
10	NO/Unknown	0.025	1.025	0.829-1.269	0.820	0.171	1.18	0.972-1.45	0.093
11							7	0	
12									
13	Distant								
14	metastasis								
15	No	Reference				Reference			
16	Yes	0.881	2.414	1.842-3.163	<0.001	1.252	3.49	2.741-4.46	<0.00
17							7	0	1
18	LNE	-0.012	0.988	0.971-1.006	0.200	-0.013	0.98	0.972-1.00	0.091
19							7	2	
20	LNP	0.062	1.064	1.022-1.107	0.002	0.069	1.07	1.032-1.11	<0.00
21							2	3	1
22	LNR	0.627	1.873	1.435-2.445	<0.001	0.934	2.54	1.965-3.29	<0.00
23							4	4	1
24									
25									
26									
27									

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.

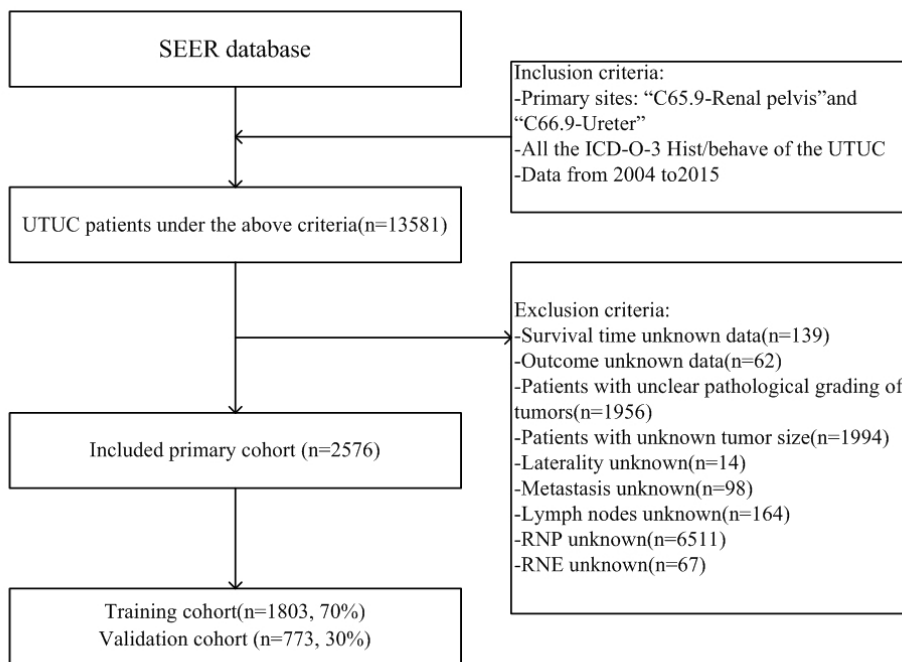


Figure 1. Data selection flowchart.

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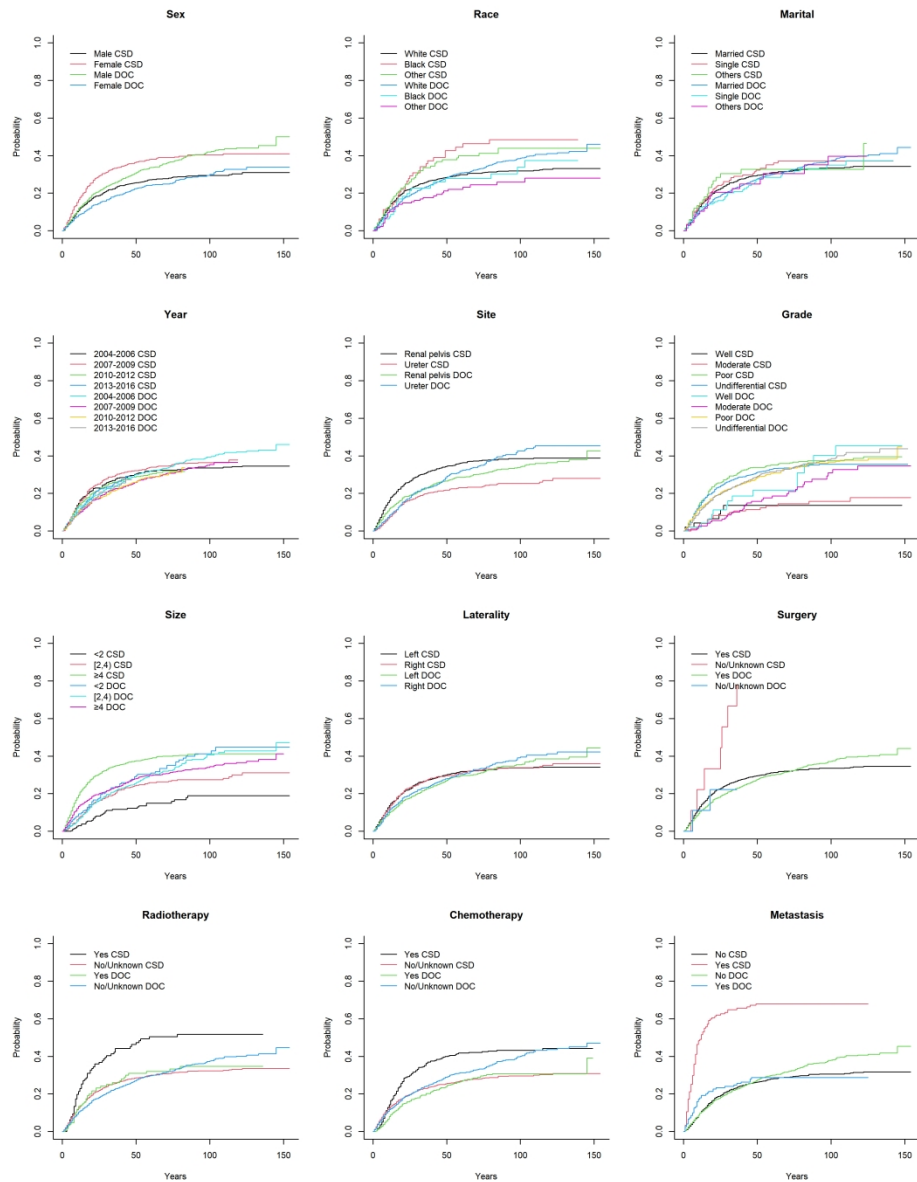


Figure 2. The CIF curves of CSD and DOC among UTUC patients.
 Abbreviations: CIF, cumulative incidence function; CSD, cancer-specific death; DOC: death due to other causes; UTUC, upper-tract urothelial carcinoma.

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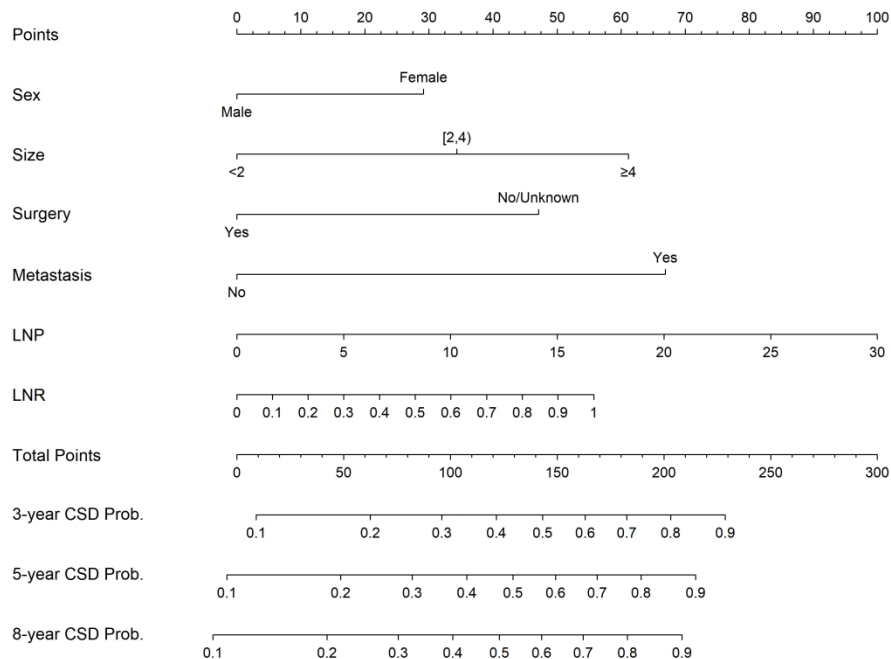


Figure 3. Nomogram based on the competing risk analysis to predict CSD probabilities at 3, 5, and 8 years for UTUC patients.

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

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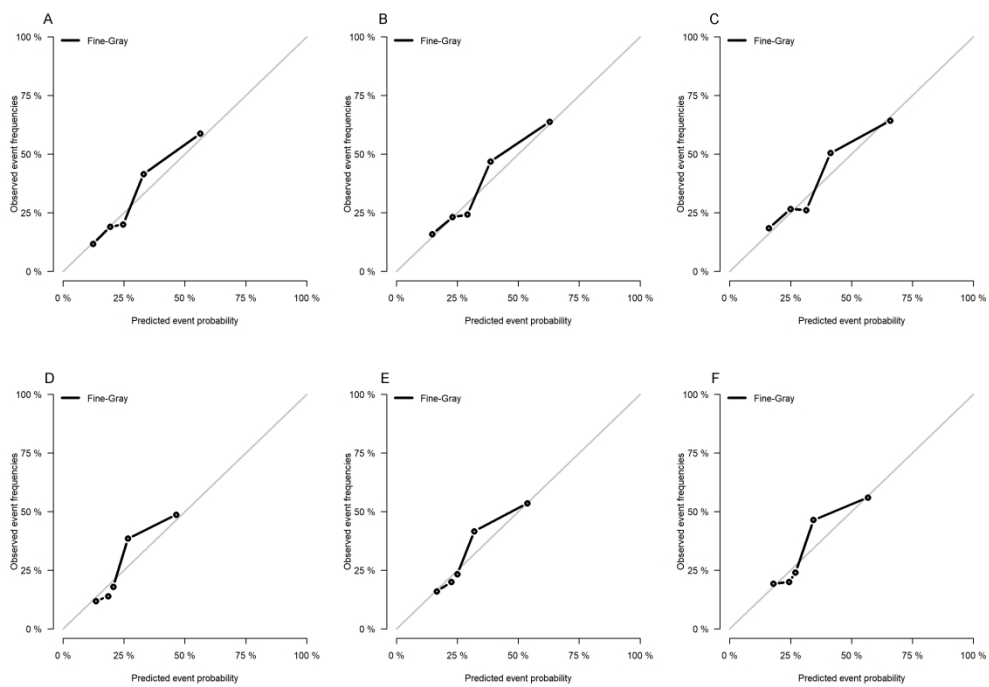


Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years of the training (A, B, C) and validation (D, E, F) cohorts.

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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, if applicable.		
	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 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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4 **A competing-risks nomogram for predicting cancer-specific death in**
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6 **upper-tract urothelial carcinoma: a population-based analysis**
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9 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

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4 metastasis, surgery status, LNP and LNR were associated with CSD. The nomogram
5
6 predicts the probability of CSD in UTUC patients at 3, 5, and 8 years, which may help
7
8 clinicians to predict the survival probabilities in individual patients.
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11 **Strengths and limitations of this study:**

- 12 •The study established the first competing risk nomogram for predicting the 3-, 5-,
13
14 and 8-year specific mortality probability for UTUC based on a large retrospective
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16 sample, which can improve the ability of clinicians to predict the survival
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18 probabilities in individual patients.
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- 21 •The established model is not comprehensive enough, because the SEER database
22
23 does not include all prognostic factors for UTUC.
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- 26 •The data available on the treatment status are not sufficiently detailed to distinguish
27
28 the impact of various treatment plans.
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- 31 •The model requires prospective studies to confirm its reliability.
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37 **Keywords:** competing risk model, upper-tract urothelial carcinoma(UTUC),
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39 nomogram, SEER, cancer-specific death
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42 **Abbreviations:** UTUC: upper-tract urothelial carcinoma; CSD: cancer-specific death;
43
44 DOC: death due to other causes; SEER: Surveillance, Epidemiology, and End
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46 Results; LNE: lymph nodes examined; LNP: lymph nodes positive; K-M:
47
48 Kaplan-Meier; CIF: cumulative incidence function; ICD-O-3: International
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50 Classification of Diseases for Oncology-3; LNR: lymph nodes ratio; C-index:
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52 concordance index; CS: cause-specific hazards model; SD: proportional
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54 subdistribution hazards model
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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

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4 cumulative incidence function (CIF) of UTUC cancer-specific death (CSD) needs to
5
6 be calculated, and prognostic factors for UTUC analyzed using the Fine-Gray
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8 proportional subdistribution hazards model [11].
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11 A nomogram is based on a prognostic model and graphically represents the
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13 predictive abilities of different prognostic factors as the lengths of line segments.
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15 This format makes it easy for clinicians to make rapid and comprehensive decisions
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17 and predict the probability of CSD, which has great clinical significance. Some
18
19 studies have constructed competing-risks nomograms for cancers such as sarcoma
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21 and prostate cancer [12, 13], but there is a lack of studies related to the UTUC.
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27 The purpose of our research was to identify the prognostic factors of UTUC
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29 based on the competing risks model and used them to construct a nomogram to
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31 predict the survival rates of patients at the 3, 5, and 8 years.
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35 **Methods**

36 **Database and patients**

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38 The Surveillance, Epidemiology, and End Results (SEER) program has yielded a
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40 database of all cancer patients in 18 defined geographic regions of the United States
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42 collected by the National Cancer Institute. It is the largest cancer registry in the
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44 United States, including information on approximately 28% of the United States
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46 population. The SEER research data is publicly available; therefore, no informed
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48 consent or institutional review board approval is required when analyzing the data.
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50 We additionally requested chemotherapy data for inclusion in our research and
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52 obtained a license for using SEER software [14, 15].
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4 We selected UTUC patients from the latest edition of the SEER database from
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6 1975 to 2016. The primary sites were extracted using the SEER codes of
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8 “C65.9-Renal pelvis” and “C66.9-Ureter.” Patients between 2004 and 2015 were
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10 included in the study. We included all of the histological subtypes of UTUC,
11
12 according to the ICD-O-3 (third revision of the International Classification of
13
14 Diseases for Oncology). The following demographic indicators were selected: age at
15
16 diagnosis, sex, race, and marital status. The primary site, histological grade, tumor
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18 size, laterality, distant metastasis, surgery status, radiotherapy status, chemotherapy
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20 status, number of lymph nodes examined (LNE), lymph nodes positive (LNP), and
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22 lymph nodes ratio (LNR; calculated as the number of LNP divided by LNE) were also
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24 included as pathological characteristics. The tumor size was divided into three groups:
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26 <2, 2–4, and ≥ 4 cm [1, 16]. The study outcomes included CSD and death due to other
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28 causes (DOC). The survival time was reported in the available data in months.
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37 **Exclusion criteria**

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40 Our preliminary selection of the above methods initially identified 13,581
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42 patients. Then, to ensure the study's accuracy, the exclusion criteria for the study data
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44 are as follows: unknown histological grade, unknown tumor size, and unknown lymph
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46 nodes status. The specific data selection process is shown in Figure 1. We finally
47
48 chose 2576 patients for inclusion in follow-up investigations.
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52

53 Figure 1

54 **Statistical methods**

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57 We randomly divided the 2576 eligible patients into 2 groups using R software
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4 (version 3.5.3, The R Foundation for Statistical Computing, Vienna, Austria;
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6 <http://www.r-project.org>): 70% (n=1803) in the training cohort and 30% (n=773) in
7
8 the validation cohort. We first described the basic composition of each factor in the
9
10 two patient cohorts using R software. The age, LNE, LNP and LNR were expressed
11
12 as median and interquartile-range values, while categorical variables were represented
13
14 as percentages. We evaluated differences in patient characteristics between two
15
16 groups using the Student's t-test and Chi-square test.
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22 We used the cumulative incidence function (CIF) to describe the probability of
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24 each event and also plotted the corresponding CIF curves. Moreover, Gray's test was
25
26 used for univariate analysis to estimate the difference in CIF between groups.
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28 Significant variables ($P < 0.05$) were included in the multivariate regression model.
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30 The Fine-Gray proportional sub-distribution hazards model was used for the
31
32 multivariate analysis and compared with the results of the cause-specific hazards
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34 model. Applying the standard Cox regression method ignores the presence of
35
36 competing risks and hence overestimates the actual incidence of beneficial events,
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38 leading to inappropriate risk stratification [17]. Several studies have confirmed that
39
40 different approaches can be used in competing-risks settings for multivariate survival
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42 analysis. However, proportional subdistribution hazards model is the best method to
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44 predict the survival probability [18-20].
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53 Finally, the results of Fine-Gray proportional sub-distribution hazards model
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55 were used to construct a nomogram of the 3, 5, and 8 years CSD rates. We used the
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57 concordance index (C-index) and calibration plots to evaluate the differentiation
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4 ability and consistency of the established model in training and validation cohorts.
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6 All statistical tests were conducted using R software (version 3.5.3). Probability
7 values of $P < 0.05$ were considered statistically significant, and all tests were
8 two-sided. The SEER database can be accessed free of charge, and this study was
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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%

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

10 11 **Construction and verification of the nomogram**

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14 Figure 3 shows the nomogram constructed according to the results of the
15 Fine-Gray proportional subdistribution hazards model for predicting the CSD
16 probabilities at 3, 5, and 8 years. LNP had the most significant impact on the
17 probability of CSD, followed by distant metastasis, tumor size, LNR, surgery, and sex
18 (Figure 3).
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27 We used both the training and validation cohorts to verify the nomogram after
28 establishing it. The 3-, 5-, and 8-years C-indexes were 0.719, 0.702, and 0.692 for the
29 training cohort, respectively, and 0.701, 0.675, and 0.668 for the validation cohort. All
30 of these values exceeded 0.6, indicating that the model had good discrimination
31 ability. We then tested the prediction accuracy of the model. As shown in Figure 4,
32 the 3-, 5-, and 8-years calibration plots for both cohorts were very close to the
33 standard straight line, demonstrating that the model was well-calibrated.
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Figures 3, 4

46 47 **Discussion**

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

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6 The application of study criteria resulted in the inclusion of 2576 patients from
7
8 the SEER database, and 1542 of these patients died during the follow-up. However,
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10 only 750 of the deaths were related to UTUC. These results indicate that the number
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12 of DOC patients was almost the same as that for CSD. In this situation, if the
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14 traditional K-M or Cox survival analysis had been adopted, the DOC patients will be
15
16 regarded as censored. This will lead to an overestimation of the cumulative incidence
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18 of CSD, which cannot truly reflect the prognosis [22, 23]. We overcame this
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20 shortcoming by using a competing risks model, which can adequately address the
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22 situation where the available data are related to multiple potential outcomes [24]. This
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24 method was first proposed by Fine and Gray and applied in previous studies [17,25–
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26 26]. In the case of competing risks, there are usually two models. One is the
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28 cause-specific hazards model (CS), the other is the proportional sub-distribution
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30 hazards model (SD), also known as the Fine-Gary model. In the present study, two
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32 models were analyzed and compared. CS is suitable for answering etiological
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34 questions, and SD is suitable for establishing clinical prediction models and risk
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36 scores. Therefore, we used the CIF and the proportional sub-distribution hazards
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38 model to explore the impact of various factors on the prognosis of CSD.
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50 The univariate analysis results showed that age, sex, race, primary site,
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52 histological grade, tumor size, surgery status, radiotherapy status, chemotherapy
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54 status, distant metastasis, LNE, LNP, and LNR were influencing factors for CSD,
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56 while age, sex, histological grade, chemotherapy status, and LNR were influencing
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4 factors for DOC. The cause-specific hazards model results showed that age, sex,
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6 histological grade, tumor size, distant metastasis, LNP, and LNR were prognostic
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8 factors for CSD. The proportional sub-distribution hazards model showed that sex,
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10 tumor size, surgery, distant metastasis, LNP, and LNR are independent prognostic
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12 factors for CSD.
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17 Age is generally considered to be a prognostic factor for most cancers, and also
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19 for UTUC [27, 28]. Our CS model showed that age was a predictor of CSD; however,
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21 it was not statistically significant in the SD model. This may be because the effect of
22
23 age on DOC is higher than the CSD; namely, elderly patients are more likely to die of
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25 other causes, which competitively leads to the fact that CSD incidence does not
26
27 increase significantly with age. Sex and race have always been controversial
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29 prognostic factors. A previous study showed that race was a preoperative prognostic
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31 factor for UTUC patients [29]. Moreover, another study found no statistically
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33 significant differences in survival between males and females [30]. However, the
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35 competing-risks model in our study showed that sex was a risk factor for UTUC,
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37 while race was not. This may be because previous studies ignored the effect of
38
39 competing risks. However, since most of the patients included in the SEER database
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41 are white; therefore, studies on different races need to be conducted.
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51 Tumor size is also considered to be related to cancer prognosis. One study found
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53 5-year recurrence-free survival rates for UTUC patients with tumor sizes <3 cm and
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55 ≥ 3 cm of 46.9% and 25.8%, respectively [31]. The univariate and multivariate
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57 analyses performed in the present study also indicated that tumor size was an
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4 influencing factor for CSD. The prognosis was worse for tumors larger than 2 cm. In
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6 addition, our research also found that distant metastasis was an important risk factor
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8 for CSD. In terms of treatment methods, our study suggested that surgery status was a
9
10 significant prognostic factor, which was consistent with the findings of Yuval et al.
11
12 [32]. Surgery has long been considered the gold standard of UTUC treatment.
13
14 However, radiotherapy status and chemotherapy status were not influencing factors
15
16 for CSD in both competing risks models. This result conflicted with some previous
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18 findings, [33–35] suggesting that traditional Cox regression analysis overestimated
19
20 the effects of radiotherapy and chemotherapy. Obviously, the relative lack of
21
22 information on the radiotherapy status and chemotherapy status in the SEER database
23
24 may also lead to inaccurate results, and thus further exploration of these indicators is
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26 needed.
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35 Some indicators related to lymph nodes (e.g., distant lymph node metastasis,
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37 LNP, and LNE) are important clinical information for cancer prognosis, but whether
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39 they are independent prognostic factors for UTUC has not been determined. One
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41 study found that lymph node metastases were significantly associated with reduced
42
43 cancer-specific survival in univariate analysis [36]. It is worth noting that very few
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45 studies have investigated LNP, LNE, and LNR. Our study is the first to use the SEER
46
47 database to analyze the prognostic impact of these indicators on UTUC, and the
48
49 results may be more accurate than those involving small samples. LNR is an emerging
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51 indicator that has been regarded as a prognostic factor in rectal cancer and breast
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53 cancer [37, 38]. Our results also suggested that LNR was an important prognostic
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4 factor of UTUC. We found that LNE was an influencing factor for UTUC in the
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6 univariate analysis but not in the multivariate analysis. Moreover, both LNR and LNP
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8 entered the proportional sub-distribution hazards model, suggesting that after
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10 adjusting for the effects of LNR and LNP, LNE was no longer an independent
11
12 prognostic indicator. LNP was a prognostic factor in all of the analyses, indicating
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14 that it significantly influences the prognosis of UTUC.
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20 We utilized the results from the above-mentioned proportional sub-distribution
21
22 hazards model to construct a nomogram that graphically represents the degrees of
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24 influence of various prognostic factors. This nomogram can be used to predict the 3-,
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26 5-, and 8-years probabilities of CSD in UTUC patients. The predictive function of the
27
28 nomogram has been used for different types of cancer and has even been proposed as
29
30 a new standard. The nomogram is easy to use. In order to calculate the CSD
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32 probability of a UTUC patient, find the patient's sex (Male or Female) on the sex row,
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34 draw a vertical line on the dot row, and get the sex score value. Repeat the above
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36 steps for tumor size, M stage, surgery, LNP, and LNR. Add the score values of each
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38 variable, find the total point on the total point axis, and draw a straight downward line
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40 to get the 3, 5, and 8 years CSD probability of the UTUC patient. For example, a
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42 female (30 points), with a tumor size of 1.5cm (0 points), at M1 stage (68 points), had
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44 performed surgery (0 points), LNP equal to 5 (15 points), and LNR equal to 0.8 (45
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46 points), the total score is 158 points, which corresponds to 3, 5, and 8 years CSD
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48 probability of 58%, 64%, and 69%, respectively.
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58 The C-indexes for the nomogram all exceeded 0.6, demonstrating that the model
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4 provided a good fit to the available data. The prediction calibration curves in Figure 4
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6 were very close to the standard curve, indicating that the nomogram had good
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8 predictive ability. The results for the validation cohort also showed that the model was
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10 stable. Therefore, this model can help clinicians to quickly and easily determine the
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12 prognosis of individual patients and provide guidance in their clinical
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14 decision-making. However, the stability of the model needs further verification.
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20 Our study used the large sample size and high-quality data from SEER database
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22 and competing risks model, which provided a guarantee for the accuracy of our study.
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24 However, inevitably, our research had some limitations. First, the established model is
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26 not comprehensive enough because the SEER database does not include all prognostic
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28 factors for UTUC. Second, the data available on the treatment status are not
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30 sufficiently detailed to distinguish the impact of various treatment plans. Third, as a
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32 retrospective study, our results may be affected by confounding bias to some extent,
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34 so the conclusion needs to be further verified in future prospective studies. Fourth, the
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36 cause of death in SEER is that some deaths may have been misclassified according to
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38 the death certificate report, which may also bring information bias to our study.
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45 **Conclusions**

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48 In summary, this study used a competing-risks model to determine the prognostic
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50 factors for UTUC. The proportional sub-distribution hazards model showed that sex,
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52 tumor size, surgery, distant metastasis, LNP, and LNR were associated with CSD,
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54 while LNE was not. The constructed nomogram can predict the 3, 5, and 8 years CSD
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56 probabilities of patients based on these relevant factors, which can support clinicians
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4 to make better decisions of the survival rates of individual patients.
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12
13 constructive advice.
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15 **Footnotes**

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19
20
21 FSX collected and analyzed the data; CZL and XL drafted the initial manuscript;
22
23
24 FFZ, and XJF reviewed and edited the article; All authors read and approved the
25
26
27 final manuscript.
28

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33

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35

36 **Data availability statement:** No additional data available
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39 **Patient consent for publication:** Informed consent were not required in current study
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41
42 because SEER research data is publicly available and all patient data are de-identified.
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44 **Ethics statement:** All procedures performed in the present study were in accordance
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47 with the principles outlined in the 1964 Helsinki Declaration and its later
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50 amendments. Institutional review board approval and informed consent were not
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53 required in current study because SEER research data is publicly available and all
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56 patient data are de-identified.

57 **Licence statement:** Other than as permitted in any relevant BMJ Author's Self
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Table 1 The basic characteristics of the patients in this study.

Variables	Training Cohort	Validation Cohort	<i>p</i>
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.

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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)	

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5	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)		
6	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)		
7	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)		
8									
9	Size				<0.001				0.733
10	<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)		
11	[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)		
12	≥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)		
13									
14	Laterality				0.944				0.393
15	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)		
16	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)		
17									
18	Surgery				0.001				0.980
19	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)		
20	NO/Unknown	77.778(76.910-78.646)	—	—	22.222(21.522-22.923)	—	—		
21									
22	Radiotherapy				<0.001				0.910
23	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)		
24	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)		
25									
26	Chemotherapy				<0.001				0.003
27	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)		
28	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)		
29									
30	Distant metastasis				<0.001				0.641
31	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)		
32	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)		
33									
34	LNE	—	—	—	<0.001	—	—	—	0.941
35	LNP	—	—	—	<0.001	—	—	—	0.448
36	LNR	—	—	—	<0.001	—	—	—	<0.001
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6 Abbreviations: CSD, cancer-specific death; DOC, death due to other causes; UTUC, upper-tract urothelial carcinoma; CI, confidence interval;
7 LNE, lymph nodes examined; LNP, lymph nodes positive; LNR, lymph nodes ratio.
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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	<i>P</i>	Coefficient	csHR	95%CI	<i>P</i>
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								

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4	Yes	Reference				Reference			
5	NO/Unknown	-0.219	0.803	0.594-1.087	0.160	-0.240	0.78	0.595-1.04	0.092
6							7	0	
7									
8	Chemotherapy								
9	Yes	Reference				Reference			
10	NO/Unknown	0.025	1.025	0.829-1.269	0.820	0.171	1.18	0.972-1.45	0.093
11							7	0	
12									
13	Distant								
14	metastasis								
15	No	Reference				Reference			
16	Yes	0.881	2.414	1.842-3.163	<0.001	1.252	3.49	2.741-4.46	<0.00
17							7	0	1
18	LNE	-0.012	0.988	0.971-1.006	0.200	-0.013	0.98	0.972-1.00	0.091
19							7	2	
20	LNP	0.062	1.064	1.022-1.107	0.002	0.069	1.07	1.032-1.11	<0.00
21							2	3	1
22	LNR	0.627	1.873	1.435-2.445	<0.001	0.934	2.54	1.965-3.29	<0.00
23							4	4	1
24									
25									
26									
27									

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.

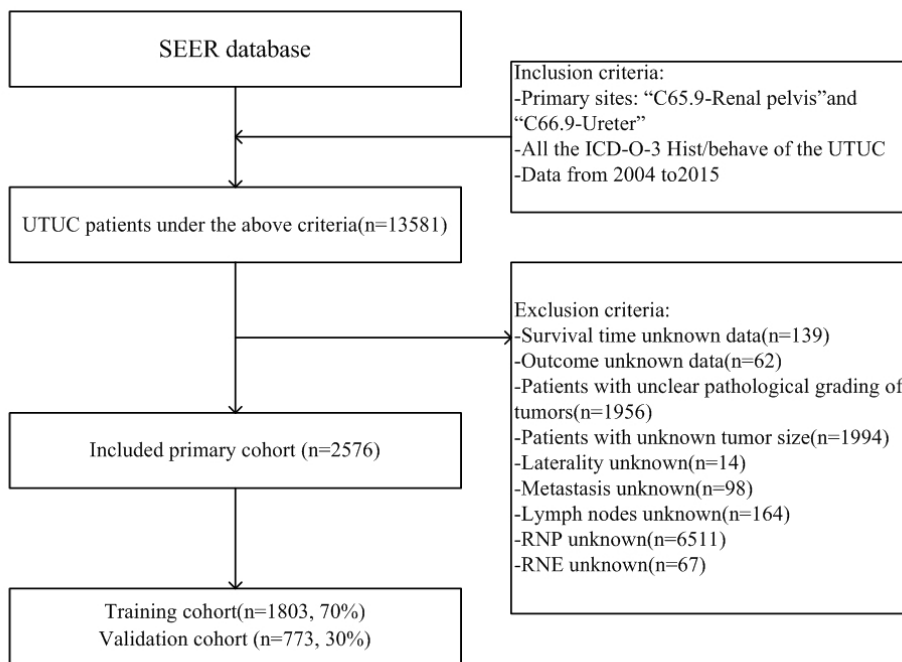


Figure 1. Data selection flowchart.

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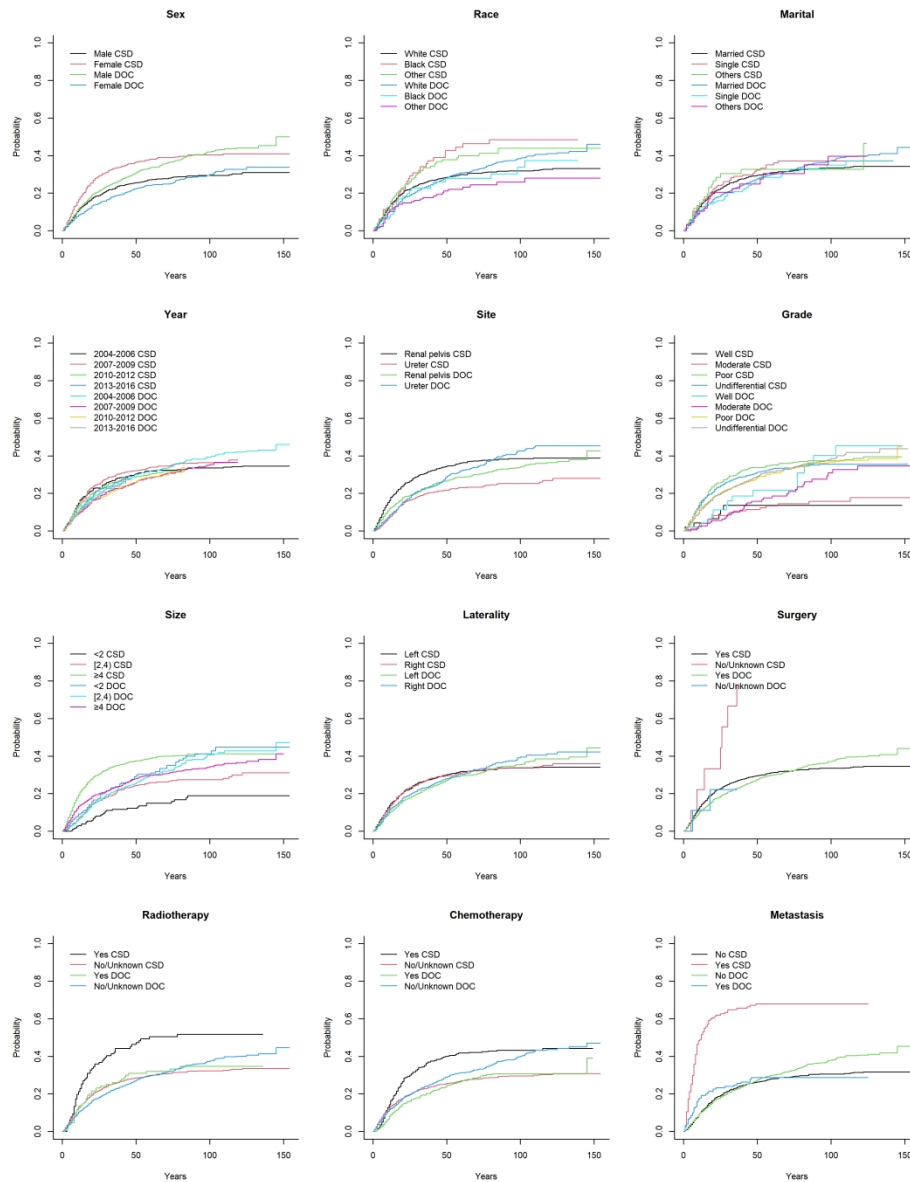


Figure 2. The CIF curves of CSD and DOC among UTUC patients. Abbreviations: CIF, cumulative incidence function; CSD, cancer-specific death; DOC: death due to other causes; UTUC, upper-tract urothelial carcinoma.

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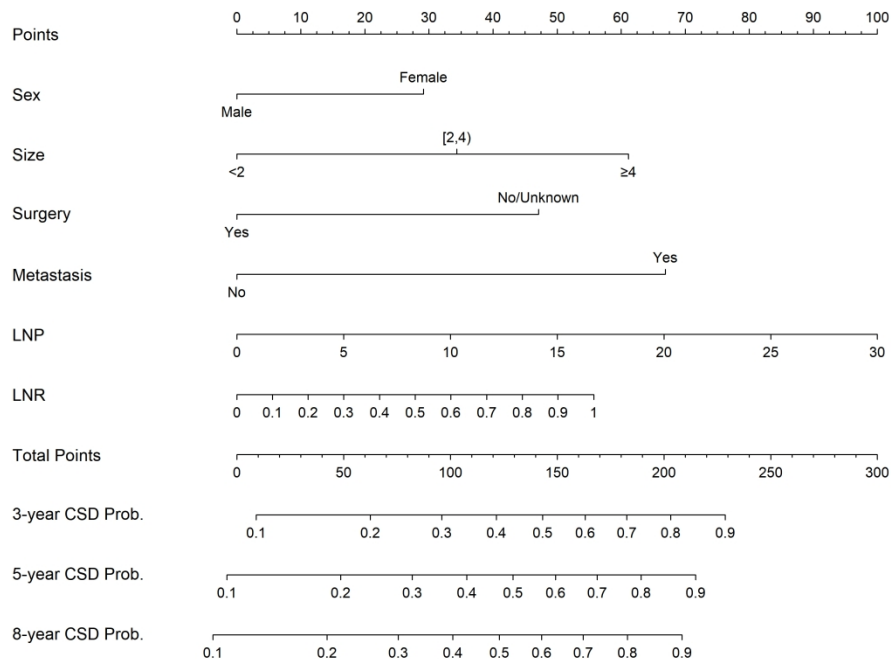


Figure 3. Nomogram based on the competing risk analysis to predict CSD probabilities at 3, 5, and 8 years for UTUC patients.

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

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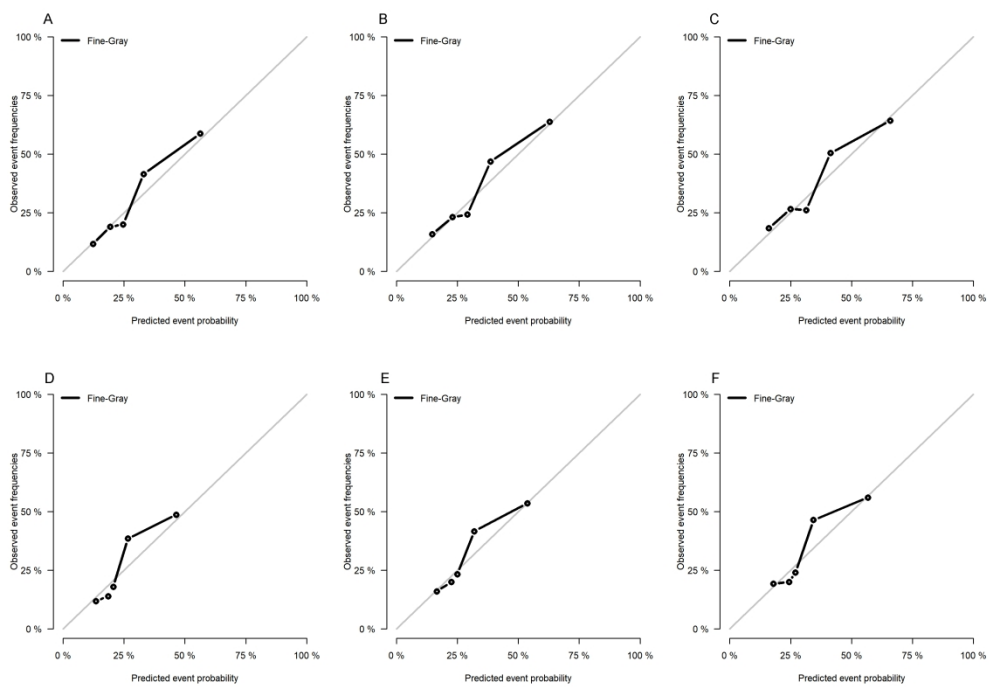


Figure 4. Calibration curves. Calibration curves for 3, 5, and 8 years of the training (A, B, C) and validation (D, E, F) cohorts.

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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, if applicable.		
	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 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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