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Nomograms for predicting overall and cancer-specific survival of patients with chromophobe renal cell carcinoma after nephrectomy: a retrospective SEER-based study

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ABSTRACT

Objective We aimed to construct and validate nomograms to predict overall survival (OS) and cancer-specific survival (CSS) for patients with chromophobe renal cell carcinoma (chRCC) after nephrectomy.

Design This study is a retrospective cohort study.

Setting and participants There were 2810 patients with chRCC from Surveillance, Epidemiology and End Results database diagnosed between 2010 and 2015 included in the study who were randomly divided into a training cohort (n=1970) and a validation cohort (n=840). Another single-centre external validation cohort containing 124 patients from our hospital was also involved in our study.

Primary and secondary outcome measures OS and CSS.

Results Nomograms for OS and CSS include four and five variables, respectively, from the result of least absolute shrinkage and selection operator regression analyses. Nomograms reveal the accurate discrimination by the area under the curve of receiver operating characteristic (ROC) curves and C-indexes, with a C-index value of 0.777 (95% CI 0.728 to 0.826), 0.810 (95% CI 0.747 to 0.873) and 0.863 (95% CI 0.773 to 0.953) for the training cohort, the internal validation cohort and the external validation cohort in the nomogram for OS; and a C-index value of 0.884 (95% CI 0.829 to 0.939), 0.868 (95% CI 0.772 to 0.964) and 0.862 (95% CI 0.760 to 0.964) for the training cohort, the internal validation cohort and the external validation cohort in the nomogram for CSS. It was also proven that there was a high degree of conformance between the predicted and observation results by calibration plots. In addition, the comparison of ROC curves and C-indexes between nomograms and seventh tumour, node and metastasis stage demonstrated that nomograms were better in accuracy and efficacy ability.

Conclusions We successfully constructed two accurate and effective nomograms to predict OS and CSS for patients with chRCC after nephrectomy, which can help clinical doctors choose individual treatment strategies for chRCC patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Surveillance, Epidemiology and End Results (SEER) database is a large database with sufficiently large samples.
⇒ There is an external validation cohort in our study to increase the reliability of our study.
⇒ The external validation cohort in our study is from single centre and the sample is not large enough.
⇒ SEER database lacks laboratory test data, which may influence the prognosis of patients with chromophobe renal cell carcinoma.

INTRODUCTION

Renal cell carcinoma (RCC) is one of the most frequently diagnosed cancers with an increasing incidence worldwide.[1] Chromophobe RCC (chRCC) accounts for 5% of all different subtypes of RCC, following clear cell RCC (ccRCC) with the incidence of 75% and papillary RCC with the incidence of 10% in the percentage of incidence.[2] ChRCC can also be classified into three subtypes: classic, eosinophilic and mixed chRCC.[3]

The treatment of RCC is different between metastatic RCC (mRCC) and non-metastatic RCC (nmRCC). For nmRCC, the primary treatment method is operation treatment[4]; on the other hand, for mRCC, the main treatment method is the use of drugs such as mTOR inhibitors,[5] c-Kit inhibitors[6] and tyrosine kinase inhibitors.[7] Considering that chRCC has the lowest risk of developing metastasis among all subtypes in RCC,[8] most chRCC patients need to undergo surgical treatment to obtain a cure. It is necessary to identify prognostic factors for patients with chRCC undergoing nephrectomy to obtain a more appropriate treatment strategy for patients with different conditions.

Currently, the tumour, node and metastasis (TNM) staging system is the most common staging system used in the prognosis

Table 1 Baseline demographic and clinicopathological information of patients with chRCC after nephrectomy in the training cohort and two validation cohorts

Variables	SEER database n (%)	Training cohort n (%)	Internal validation cohort n (%)	External validation cohort n (%)
Total	2810 (100)	1970 (100)	840 (100)	124 (100)
Age, years				
<61	1567 (55.8)	1097 (55.7)	470 (56.0)	89 (71.8)
61–74	950 (33.8)	669 (33.9)	281 (33.4)	31 (25.0)
>74	293 (10.4)	204 (10.4)	89 (10.6)	4 (3.2)
Race				
White	2275 (81.0)	1576 (80.0)	699 (83.2)	0 (0)
Black	358 (12.7)	271 (13.8)	87 (10.4)	0 (0)
Other	177 (6.3)	123 (6.2)	54 (6.4)	124(100)
Sex				
Male	1521 (54.1)	1051 (53.4)	470 (56.0)	60 (48.4)
Female	1289 (45.9)	919 (46.6)	370 (44.0)	64 (51.6)
Grade				
Grade I	146 (5.2)	97 (4.9)	49 (5.8)	4 (3.2)
Grade II	959 (34.1)	683 (34.7)	276 (32.9)	37 (29.8)
Grade III	572 (20.4)	413 (21.0)	159 (18.9)	21 (16.9)
Grade IV	120 (4.3)	80 (4.0)	40 (4.8)	6 (4.9)
Unknown	1013 (36.0)	697 (35.4)	316 (37.6)	56 (45.2)
AJCC stage				
I	1815 (64.6)	1264 (64.2)	551 (65.6)	95 (76.6)
II	536 (19.1)	379 (19.2)	157 (18.7)	20 (16.1)
III	419 (14.9)	303 (15.4)	116 (13.8)	8 (6.5)
IV	40 (1.4)	24 (1.2)	16 (1.9)	1 (0.8)
T stage				
T1	1824 (64.9)	1272 (64.6)	552 (65.7)	93 (75.0)
T2	551 (19.6)	390 (19.8)	161 (19.2)	22 (17.7)
T3	429 (15.3)	307 (15.5)	122 (14.5)	9 (7.3)
T4	6 (0.2)	1 (0.1)	5 (0.6)	0 (0)
N stage				
N0	2776 (98.8)	1943 (98.6)	833 (99.2)	123 (99.2)
N1	34 (1.2)	27 (1.4)	7 (0.8)	1 (0.8)
M stage				
M0	2776 (98.8)	1947 (98.8)	829 (98.7)	123 (99.2)
M1	34 (1.2)	23 (1.2)	11 (1.3)	1 (0.8)
SEER stage				
Localised	2350 (83.6)	1642 (83.4)	708 (84.3)	106 (85.5)
Regional	424 (15.1)	305 (15.4)	119 (14.2)	17 (13.7)
Distant	36 (1.3)	23 (1.2)	13 (1.5)	1 (0.8)
Surgery				
Partial nephrectomy	1195 (42.5)	830 (42.1)	365 (43.5)	46 (37.1)
Total nephrectomy	1615 (57.5)	1140 (57.9)	475 (56.5)	78 (62.9)
Tumour size, mm				
<51	1543 (54.9)	1080 (54.8)	463 (55.1)	78 (62.9)
51–108	922 (32.8)	644 (32.7)	278 (33.1)	33 (26.6)

Continued

Table 1 Continued

Variables	SEER database n (%)	Training cohort n (%)	Internal validation cohort n (%)	External validation cohort n (%)
>108	345 (12.3)	246 (12.5)	99 (11.8)	13 (10.5)
Marital status				
Married	1713 (61.0)	1217 (61.8)	496 (59.0)	85 (68.6)
Unmarried	934 (33.2)	649 (32.9)	285 (34.0)	23 (18.5)
Unknown	163 (5.8)	104 (5.3)	59 (7.0)	16 (12.9)

AJCC, American Joint Committee on Cancer; chRCC, chromophobe renal cell carcinoma; SEER, Surveillance, Epidemiology and End Results.

prediction of patients with RCC.[9] However, the TNM staging system has only some anatomical prognostic factors and does not have other potential prognostic factors, such as age, operation method and pathological grade, which may influence the prognosis of patients with chRCC undergoing nephrectomy. Hence, it is clear that a more complete and practical prognostic model is needed.

A nomogram is a statistically graphic tool used in prognosis prediction by comprising all the potential prognostic factors and calculating the risk scores of each patient to

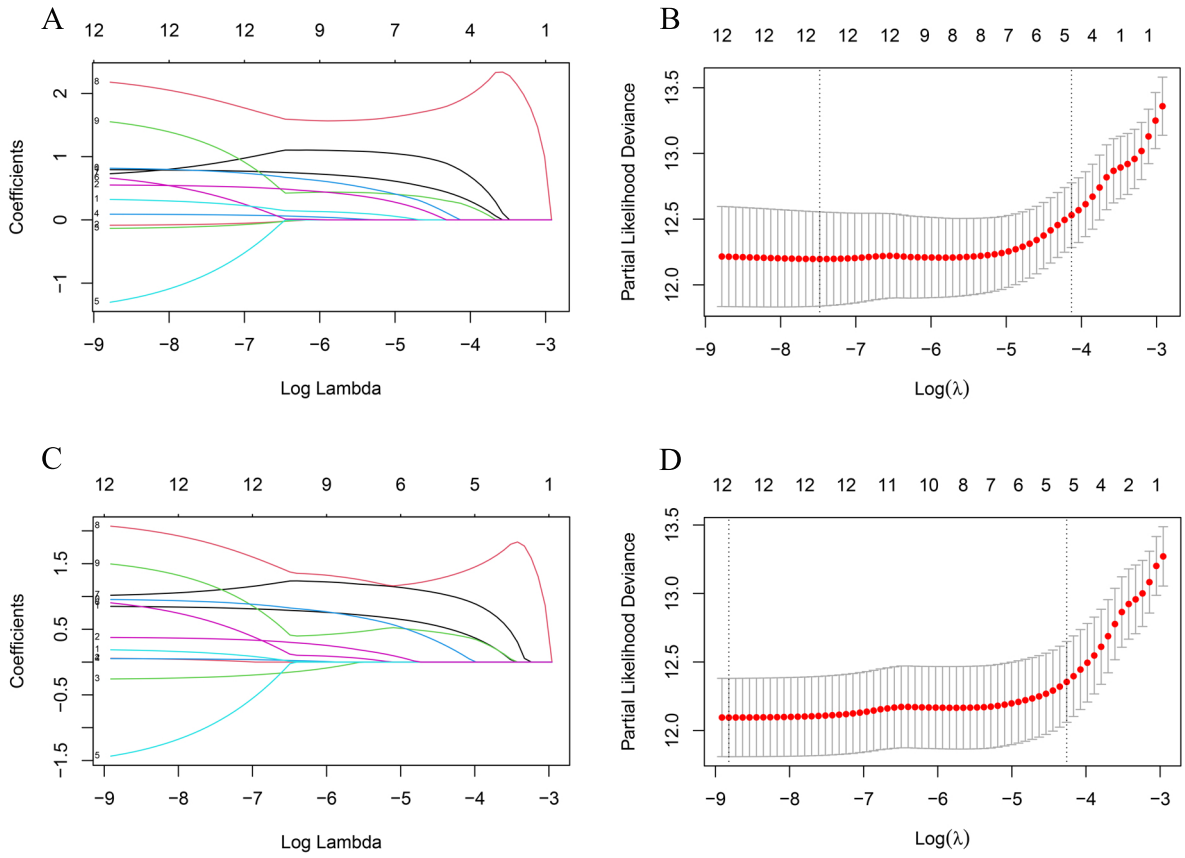

Figure 1 Variables selection in the nomogram for OS using the LASSO regression analysis with 10-fold cross-validation (A–B). (A) Tuning parameter (lambda) selection of deviance in the LASSO regression based on the minimum criteria (left dotted line) and the 1-SE criteria (right dotted line). (B) A coefficient profile plot was created against the log (lambda) sequence. Variables selection in the nomogram for CSS using the LASSO regression analysis with 10-fold cross-validation (C–D). (C) Tuning parameter (lambda) selection of deviance in the LASSO regression based on the minimum criteria (left dotted line) and the 1-SE criteria (right dotted line). (D) A coefficient profile plot was created against the log (lambda) sequence. In our study, the selection of variables was according to the 1-SE criteria (right dotted line), where 4 and 5 non-zero coefficients were selected for the nomogram of OS and CSS. CSS, cancer-specific survival; LASSO, least absolute shrinkage and selection operator; OS, overall survival.

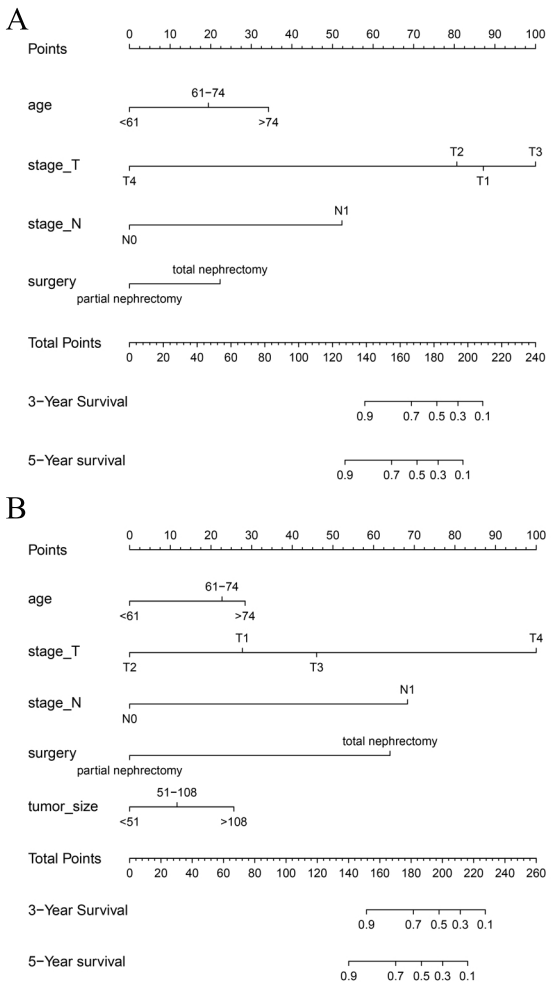

Figure 2 Constructed nomograms to predict 3-year and 5-year OS (A) and CSS (B) for patients with chRCC after nephrectomy. CSS, cancer-specific survival; chRCC, chromophobe renal cell carcinoma; OS, overall survival.

predict their survival outcomes.[10] The nomogram can help clinicians choose the right individualised treatment plan and predict the survival prognosis of each patient. Currently, various nomograms have been designed and used in the prognosis evaluation for patients with RCC, but most are for ccRCC and pRCC. Although Chen, *et al*[11] constructed a nomogram for chRCC patients, it is for all chRCC patients and it is not verified by an external validation cohort, there is still not a nomogram for chRCC patients with surgery treatment. Therefore, the purpose of our study was to construct nomograms based on data from the Surveillance, Epidemiology and End Results (SEER) database to predict overall survival (OS) and cancer-specific survival (CSS) for chRCC patients undergoing surgery and to validate the nomogram with an internal SEER cohort and an individual cohort from our department.

METHODS

Patients registration

In our study, we retrospectively collected chRCC patients after nephrectomy diagnosed between 2010 and 2015 from the SEER 18 database by using SEER*Stat software V.8.3.8, according to the International Classification of Diseases for Oncology third edition, primary site codes C64.9 and C65.9 (kidney and renal pelvis) and histological/behaviour codes 8270/0, 8270/1 and 8270/3 (chromophobe carcinoma). The inclusion criteria were as follows: (1) patients who underwent nephrectomy with explicit surgery method; (2) patients diagnosed at least 18 years old; (3) patients with active follow-up; (4) patients histologically diagnosed with the first malignant tumour; (5) patients for whom the cause of death was available; (6) patients with known clinical data and (7) survival time is at least 1 month. After screening by the above criteria, 2810 eligible patients with chRCC were included in the study. Subsequently, the patients were randomly divided into two cohorts, including the training cohort with 70% of patients (n=1970) and the validation cohort with 30% of patients (n=840). For the purpose of testing our results further, we validated them in another single-centre external validation cohort from China. There were 124 patients with chRCC after nephrectomy diagnosed between 1 September 2010 and 31 December 2020 who met the inclusion criteria above. They were all diagnosed by pathology results. The flow chart of the patient screening is shown in online supplemental figure 1.

Data collection

In our study, clinical data and follow-up information were collected by two independent researchers. The variables included age at diagnosis, race, sex, American Joint Committee on Cancer (AJCC) stage histological grade, T stage, N stage, M stage, SEER stage, surgery method, tumour size and marital status. In this study, the primary endpoints included OS and CSS. OS was defined as the time interval between diagnosis and death or last follow-up. CSS was defined as the time interval between diagnosis and death caused by chRCC or the last follow-up.

Statistical analysis

Continuous variables in our study, including age and tumour size, were divided into three categories using X-tile software (V.3.6.1, Yale University of Medicine, USA), which is useful software to calculate the optimal cut-off points for continuous data.[12] The least absolute shrinkage and selection operator (LASSO) regression was performed to screen the prognostic factors according the data from the training cohort. Variables screened by LASSO regression analyses were included in nomograms to predict 3-year and 5-year OS and CSS in patients with chRCC after nephrectomy.

Afterwards, two nomograms needed to be validated internally by a SEER validation set and externally by a

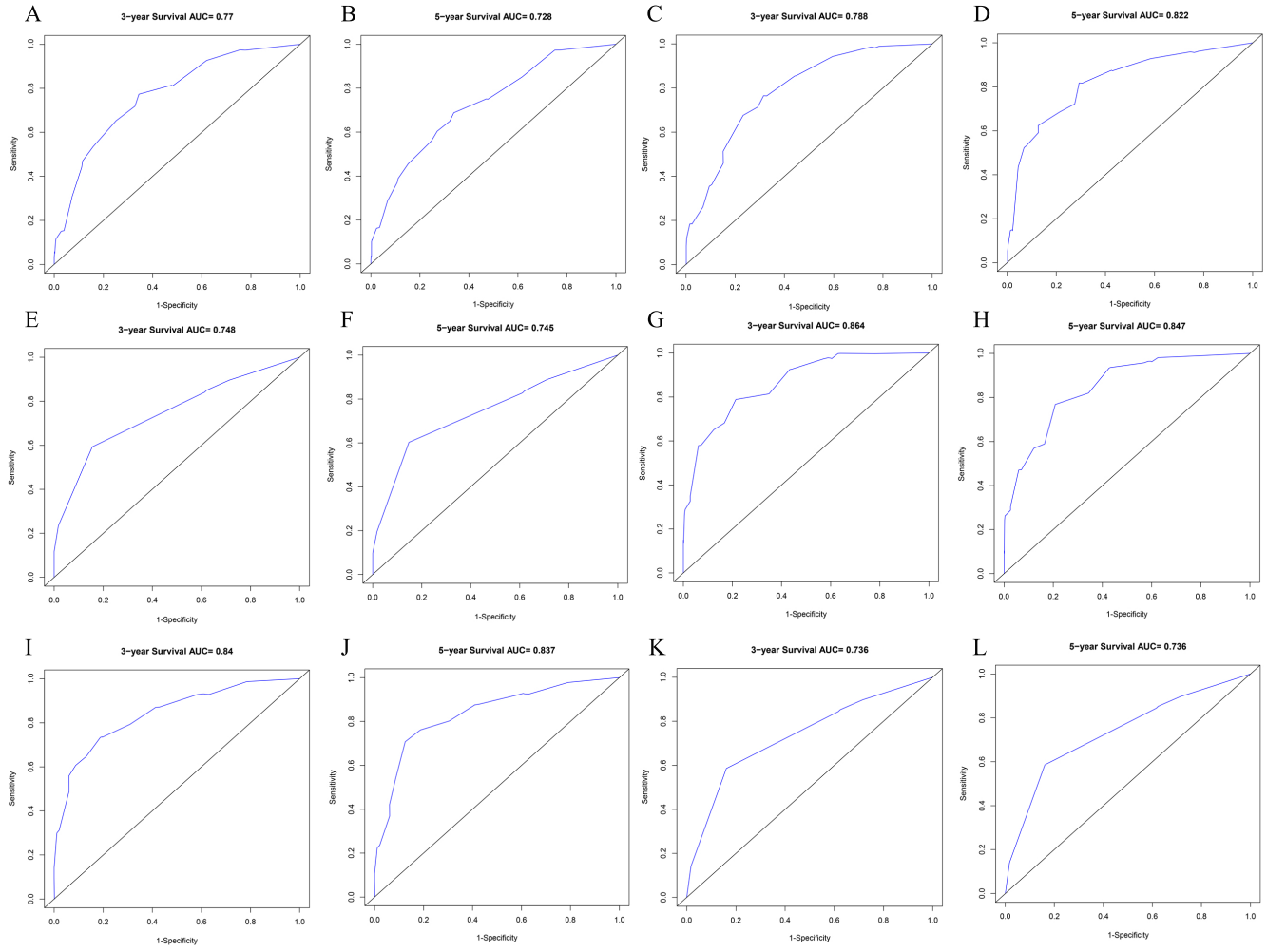

Figure 3 ROC curves of nomograms to predict OS at 3-year (A) and 5-year (B) in training cohort, at 3 years (C) and 5 years (D) in the internal validation cohort, and at 3 years (E) and 5 years (F) in the external validation cohort; CSS at 3 years (G) and 5 years (H) in training cohort, at 3 years (I) and 5 years (J) in the internal validation cohort, and at 3 years (K) and 5 years (L) in the external validation cohort. AUC, area under the curve; CSS, cancer-specific survival; OS, overall survival; ROC, receiver operating characteristic.

set in our hospital. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to evaluate the sensitivity and specificity of the two nomograms. In addition, concordance index (C-index) and calibration curves were performed to evaluate the discriminative and accuracy ability of the two nomograms.

All of the statistical analyses were performed by R V.4.1.0 (http://www.r-project.org). A $p<0.05$ (two sided) was considered statistically significant. However, our study is a retrospective study and the data are anonymous, hence the demand for informed consent was exempted.

Patient and public involvement

No patients were involved in the formulation of the study.

RESULTS

Patients characteristics

In our study, a total of 2810 patients with chRCC after nephrectomy collected between 2010 and 2015 from the SEER database were included. Data were divided into the training cohort (n=1970) and the validation cohort (n=840). Age and tumour size were divided into three categories by X-tile software. The best cut-off age was 61 years old and 74 years old (online supplemental figure 2), and the best cut-off tumour size was calculated to be 51 mm and 108 mm (online supplemental figure 3). In addition, an external Chinese single-centre validation cohort (n=124) from Shengjing Hospital was also included in our study. The demographic and clinicopathological information of the training cohort and two validation cohorts are shown in table 1.

The median follow-up time from the SEER database was 30 months (IQR 14–49). The median follow-up time from the external Chinese single-centre validation cohort was 42 months (IQR 26–71). In our study, the number of patients died in the training cohort, internal validation cohort and external validation cohort were 85, 41and 8. The number of patients dying of chRCC in the training

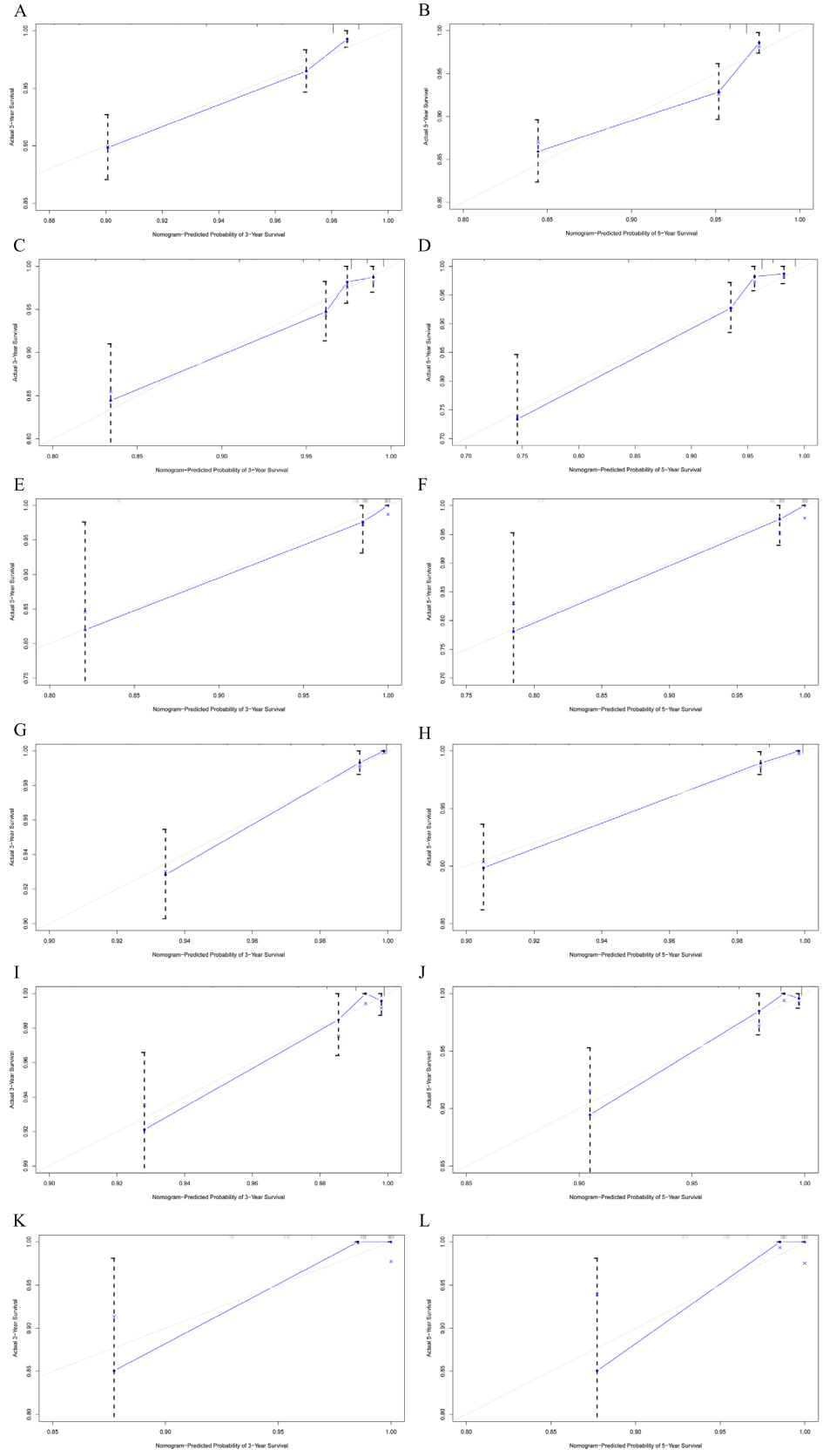

Figure 4 Calibration plots for nomograms to predict OS at 3 years (A) and 5 years (B) in training cohort, at 3 years (C) and 5 years (D) in the internal validation cohort, and at 3 years (E) and 5 years (F) in the external validation cohort; CSS at 3 years (G) and 5 years (H) in training cohort, at 3 years (I) and 5 years (J) in the internal validation cohort, and at 3 years (K) and 5 years (L) in the external validation cohort. The x-axis indicates the nomogram-predicted OS, y-axis indicates the actual OS. CSS, cancer-specific survival; OS, overall survival.

cohort, internal validation cohort and external validation cohort were 37, 19and 5. The 5-year OS and CSS rates from the SEER training cohort were 95.7% and 98.1%, respectively. The 5-year OS and CSS rates from the internal validation cohort were 95.6% and 98.0%, respectively. Additionally, for the external validation cohort, the 5-year OS and CSS rates were 94.4% and 96.0%, respectively.

Selection of risk factors by LASSO regression analyses

LASSO regression analyses were performed to select the risk factors. The results of LASSO regression analyses of OS in the training cohort were shown in figure 1A,B. From 12 variables collected from patients in table 1, 4 variables were selected based on the non-zero coefficients result. The selected variables included age, T stage, N stage and surgery method. In addition, there are five variables selected based on the non-zero coefficients based on the result of LASSO regression analyses of CSS in the training cohort (figure 1C,D). These variables contained age, T stage, N stage, surgery method and tumour size.

Construction of nomograms for predicting OS and CSS

All the variables selected through LASSO regression analyses were included to construct two nomograms to predict 3-year and 5-year OS (figure 2A) and CSS (figure 2B). Each variable was given a score on the score scale. The total score is calculated by adding up the score of all variables. Then, we used the total score to predict the 3-year and 5-year OS and CSS of patients.

Validation and calibration of OS and CSS nomograms

Two nomograms of OS and CSS were first validated by ROC curves. The 3-year and 5-year AUCs of OS were 0.770 and 0.728 (figure 3A,B) in the training cohort, 0.788 and 0.822 (figure 2C,D) in the internal validation cohort, and 0.748 and 0.745 (figure 2E,F) in the external validation cohort. The 3-year and 5-year AUCs of CSS were 0.864 and 0.847 (figure 2G,H) in the training cohort, 0.840 and 0.837 (figure 2I,J) in the internal validation cohort, and 0.736 and 0.736 (figure 2K,L) in the external validation cohort. The ROC curve results show a favourable discriminative ability for the two nomograms to predict OS and CSS.

In addition, the calibration plots of 3-year and 5-year OS in the training cohort (figure 4A,B), internal validation cohort (figure 4C,D) and external validation cohort (figure 4E,F) revealed brilliant consistency between the actual and predicted outcomes. Similarly, the calibration plots of 3-year and 5-year CSS showed excellent calibration in the training cohort (figure 4G,H), internal validation cohort (figure 4I,J) and external validation cohort (figure 4K,L). Both nomograms were calibrated well in the training set and two validation sets.

Comparison between nomograms and AJCC TNM system

Finally, two nomograms were compared with the AJCC TNM system by the C-index and ROC curve. For the nomogram of OS, the C-index results in the training group, internal validation group and external validation group were 0.777, 0.810 and 0.863, respectively, showing a better predictive ability than the AJCC TNM system, in which the C-index results in the training group, internal validation group and external validation group were 0.669, 0.660 and 0.667, respectively. Similarly, the nomogram of CSS also proved to be better based on the C-index results in the training group, internal validation group and external validation group (0.884, 0.868 and 0.862, respectively) than the C-index of the AJCC TNM system (0.823, 0.823 and 0.759, respectively). The specified C-index results between the nomograms and the AJCC TNM system are shown in online supplemental table 1). In addition, ROC curve analysis showed our nomograms had a better predictive ability for OS (online supplemental figure 4A-F) and CSS (online supplemental figure 4G-L). In summary, the C-index and ROC curve results indicate that our nomograms are more applicable than the AJCC TNM system for prognostic prediction in patients with chRCC after nephrectomy.

DISCUSSION

ChRCC is the third most frequent subtype of renal solid tumours. Unfortunately, there has been little progress in the therapeutic options for patients with chRCC over decades due to its low incidence.[13] According to the current clinical condition, most patients need surgical treatment to recover.[14 15] Therefore, nomograms to predict the survival prognosis of patients with chRCC after nephrectomy and help doctors design individual therapeutic plans are of excellent clinical significance. Here, our study used data from the SEER database to construct two nomograms with excellent predictive performance for predicting OS and CSS probability at 3 years and 5 years for patients with chRCC after nephrectomy and internally verified the nomograms by data from the SEER database and externally by an independent cohort from our hospital.

A multi-institution study carried out by Ohashi *et al*[16] concluded that age and T stage are the main independent factors of survival prognosis for patients with chRCC, which resembles our conclusions. A large single-institution study conducted by Casuscelli *et al*[17] concluded that T stage is an independent prognostic factor of OS for patients with chRCC after nephrectomy, which is similar to the findings of our study. In addition, Frees *et al*[18] also demonstrated that partial nephrectomy is an independent prognostic factor of CSS for patients with chRCC after nephrectomy, which is consistent with the results of our study. The consistency of the conclusions between our study and other previous relevant studies reveals the reliability of our study. In addition, in our study, patients 61 years old or older and patients with the tumour size of 51 mm or larger showed worse OS and CSS rates as age increased.

Presently, the AJCC TNM stage is the staging system used most frequently to predict the survival prognosis of patients and has been shown to be effective for patients

with chRCC from the study conducted by Xie *et al*.[19] However, AJCC TNM stage only contains information on the tumour size, the state of lymph node metastasis and distant site metastasis condition. Although AJCC TNM stage is absolutely relevant to prognosis, there is doubt that if other demographic and clinical information, such as age, pathological grade and treatment method, makes a difference in the survival outcomes, we designed nomograms combined with more information to predict the survival prognosis of patients with chRCC after nephrectomy. In our study, our nomograms showed better accuracy and practicability than the AJCC TNM stage according to the results of ROC curves and C-indexes, which reveals the advantage of our nomograms.

Another advantage of our study is that it constructed nomograms of OS and CSS of patients with chRCC after nephrectomy by population-based data from the SEER database with sufficiently large samples and an external validation cohort, which can increase the validity and effectiveness of our conclusions. Although one study conducted by Chen *et al*[11] also constructed nomograms of OS and CSS for patients with chRCC, our study has some differences. First, the collected data in our study are for patients after nephrectomy, and the study carried out by Chen *et al*[11] is for all patients with chRCC. Based on the truth that most patients with chRCC need nephrectomy, our study is more targeted for patients with chRCC requiring surgery treatment, which is the overwhelming majority of patients with chRCC. In addition, in our study, there was an external validation cohort, which did not exist in Chen's study. The nomograms in our study also showed reliable consistency in the external validation cohort.

However, there are still some limitations in our study. First, the SEER database lacks laboratory test data, which may influence the prognosis of patients with chRCC. Moreover, nomograms in our study does not be compared with other known RCC nomograms like Fuhrman grade and MSKCC prognostic classification because of the limited data in SEER database. Hence, comparison between our nomograms and other known nomograms needs to be completed in the future. Finally, our study is a retrospective study, and an external validation cohort with a small sample size from a single institution may decrease the accuracy and efficacy of our study. Consequently, a large multicentre prospective study will be needed to validate the accuracy of our nomograms in the future.

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Contributors JZ conceived and designed the experiments, wrote the original draft and approved the final draft. SL analysed the data, prepared figures and/or figures and approved the final draft. YZ collected the data, prepared figures and/or figures and approved the final draft. ZT collected the data, prepared figures and/or figures and approved the final draft. LL authored or reviewed the draft and approved the final draft. ZL authored or reviewed the draft and approved the final draft. ML edited the draft and approved the final draft. XC provided the funding, designed the experiments, authored or reviewed the draft, approved the final draft and was responseble for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study involved human participants and was approved by the Ethics Committee of the Shengjing Hospital of China Medical University, and in accordance with the Declaration of Helsinki of the World Medical Association. (Ethical application reference: 2019PS106K.).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The following information was supplied regarding data availability. Data are availability at Surveillance, Epidemiology and End Results (SEER) database, Primary Site-labeled: C64.9-kidney, expect renal pelvis and C65.9-renal pelvis, ICD-O-3 histology/behaviour grade-labeled: 8270/0-chromophobe adenoma, 8270/1-chromophobe adenoma, borderline and 8270/3-chromophobe carcinoma from 2010 and 2015.

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