Development and Validation of a Nomogram to Predict Overall Survival for Patients with Metastatic Renal Cell Carcinoma

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Abstract

**Background:** The prognosis of metastatic renal cell carcinoma (RCC) patients vary widely because of clinical and pathological heterogeneity. We aimed to develop a novel nomogram to predict overall survival (OS) for this population.

**Methods:** Metastatic RCC patients were selected from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2016. These patients were randomly assigned to a training set and a validation set at a ratio of 1:1. Significant prognostic factors of survival were identified through Cox regression models and then integrated to form a nomogram to predict 1-, 3- and 5-year OS. The nomogram was subsequently subjected to validations via the training and the validation sets. The performance of this model was evaluated by using Harrell’s concordance index (C-index), calibration curve, integrated discrimination improvement (IDI), net reclassification improvement (NRI), and decision curve analysis (DCA).

**Results:** Overall, 2315 eligible metastatic RCC patients were enrolled from the SEER database. A nomogram of survival prediction for patients of newly diagnosed with metastatic RCC was established, in which eight clinical factors significantly associated with OS were involved, including Fuhrman grade, lymph node status, sarcomatoid feature, cancer-directed surgery, bone metastasis, brain metastasis, liver metastasis, and lung metastasis. The new model presented better discrimination power than the American Joint Committee on Cancer (AJCC) staging system (7th edition) in the training set (C-indexes, 0.701 vs. 0.612, \(P<0.001\)) and the validation set (C-indexes, 0.675 vs. 0.600, \(P<0.001\)). The calibration plots of the nomogram exhibited optimal agreement between the predicted values and the observed values. The results of NRI and IDI also indicated the superior predictive capability of the nomogram relative to the AJCC staging system. The DCA plots revealed higher clinical use of our model in survival prediction.

**Conclusions:** We developed and validated an effective nomogram to provide individual OS prediction for metastatic RCC patients, which would be beneficial to clinical trial design, patient counseling, and therapeutic modality selection.

Background
Kidney cancer, one of the most common genitourinary malignancy, accounts for 2.2% of new cancer cases and 1.8% of cancer deaths worldwide in 2018 [1]. It is estimated that in the United States, the new cases and deaths of kidney and renal pelvis cancer in 2019 are 73820 and 14770, respectively [2]. RCC, as the most common subtype, constitutes 90%-95% of all kidney neoplasm [3]. Based on the SEER program, 16% of the kidney cancer patients presented metastatic stage at diagnosis, and 5-year relative survival was only 13.0% during 2010-2016 [4]. A study from the national Swedish kidney cancer register reported that 15%-23% of the RCC patients were diagnosed with metastatic disease at presentation between 2005 and 2010 [5].

It is vitally important to construct accurate prognostic models for clinical trial design, patient counseling, and therapeutic modality selection. At present, the most widely used prognostic models for metastatic RCC are the Memorial Sloan-Kettering Cancer Center (MSKCC) model and the International Metastatic RCC Database Consortium (IMDC) model. The MSKCC retrospectively examined 463 metastatic RCC patients enrolled in six clinical trials and administered interferon-α from 1982 to 1996. Karnofsky performance status, lactate dehydrogenase, serum hemoglobin, corrected serum calcium, and time from diagnosis to treatment were independent prognostic factors in this model [6]. Subsequently, the MSKCC model was validated in an independent cohort of 353 previously untreated metastatic RCC patients from the Cleveland Clinic [7]. In the ear of targeted therapy, Heng et al identified 645 patients with metastatic RCC treated with sunitinib, sorafenib, or bevacizumab plus interferon from the IMDC during 2004–2008, and proposed the prognostic model including Karnofsky performance status, serum hemoglobin, corrected serum calcium, time from diagnosis to treatment, neutrophils, and platelets [8]. Similarly, the two models all stratify the metastatic RCC patients based on the number of prognostic risk factors, and the median OS of each group are provided.

The metastatic RCC patients are heterogeneous with respect to clinical and pathological characteristics, and their survival varies widely [9]. Though the MSKCC and IMDC models can effectively stratify the patients into different risk groups, the patients in the same risk group may have different clinical outcomes, and a more precise model for individual survival prediction is still
vitally needed. The two models are proposed based on the patients receiving interferon-α or targeted therapy, which are not suitable for predicting the clinical outcomes of the patients with newly diagnosed metastatic RCC. Additionally, to our knowledge, no prognostic model for metastatic RCC patients is performed based on the SEER program. In this study, we aim to explore a predictive nomogram for the patients with newly diagnosed metastatic RCC by combining clinical and pathological characteristics based on the SEER program and evaluate the discrimination, calibration, and clinical use of this model.

Methods
Data source
The SEER database (http://www.seer.cancer.gov), covering approximately 28% of the US population, is used to identify the patients in our study. The SEER database can provide information freely to registered researchers, including patient demographics, primary tumor site, tumor stage, surgical treatment, patient survival data, and so on. We obtained the permission to access the database after submitting a SEER Research Data Agreement form through e-mail. The software of SEER*Stat (version 8.3.5) was used to extract the data, and our user name was 11697-Nov2018.

Study Population
The patients with metastatic RCC were identified between 2010 and 2016 using the software of SEER*Stat. Key patient eligibility criteria were as following: (1) The RCC patients who had distant metastasis at diagnosis between 2010 and 2016 were enrolled. (2) RCC was the first and only primary diagnosis. (3) All the diagnoses of RCC were confirmed by histological examination. (4) Complete follow-up data of the RCC patients could be obtained. The exclusion criteria included: age < 18 years at diagnosis, unknown follow-up data, and unknown information about race, marital status, Fuhrman grade, tumor size, tumor stage, lymph node status, metastasis, and surgery. Autopsy or death certificate cases were also excluded. Finally, a total of 2315 patients with metastatic RCC were included in this cohort. The flow diagram for patient selection was presented in Fig. 1.

Measurements Of Variables
For each patient, the demographic and clinical variables were recorded, including age at diagnosis, race (black, white, other), sex (male, female), marital status (married, unmarried), histologic subtype
(clear cell renal cell carcinoma, CCRCC; papillary renal cell carcinoma, PRCC; chromophobe renal cell carcinoma, CHRCC; sarcomatoid renal cell carcinoma, SRCC; collecting duct renal cell carcinoma, CDRCC), Fuhrman grade (grade I, grade II, grade III, grade IV, unknown), Tumor classification (T1, T2, T3, T4, TX), Lymph node status (N0, N1, NX), sarcomatoid feature (yes, no, unknown), chemotherapy (yes, no/unknown), radiotherapy (yes, no), surgery (yes, no), bone metastasis (yes, no), brain metastasis (yes, no), liver metastasis (yes, no), lung metastasis (yes, no), survival time, and vital status. The AJCC Cancer Staging Manual (7th edition, 2010) was employed to evaluate the tumor stages.

Ascertainment Of The Outcome
The primary outcome of this study was OS, which was defined as survival from diagnosis of metastatic RCC to death due to any cause. OS was ascertained based on the code “vital status” in the SEER database.

Statistical analysis
The selected patients were randomly assigned to a training set and a validation set at a ratio of 1:1. Descriptive statistics was initially performed to describe the baseline characteristics of the patients in training and validation sets. Continuous variables with normal distribution were shown as mean (standard deviation), and non-normal continuous variables were presented as median (interquartile range). Categorical variables were summarized in terms of frequency and percentages. For the training set, univariate and multivariate Cox regression modeling were performed to generate crude and adjusted hazard ratios (HRs) for identifying the significant prognostic factors of OS. The selection of prognostic factors was carried out using a backward stepwise process with the Bayesian information criterion. The proportional hazards assumption of Cox regression modeling was assessed with the use of Schoenfeld residuals. Nomograms, graphic tools to quantify risks and calculate the probability of clinical events by scoring the involved factors, had been demonstrated to generate more precise prediction than the conventional AJCC staging system in several types of cancers [10, 11]. In the current study, the nomogram for predicting 1-, 3-, and 5-year OS was formulated based on the results of multivariate
Cox regression model.

Discrimination and calibration, important properties in the evaluation of model performance, were both assessed in our study. C-index was applied to evaluate the discriminative ability of the nomogram, which depicted the probability of the predicted risk was higher for a random patient having an event than for a random patient not having an event. After comparing the predicted probability of events for all possible pairs of patients, C-index was 0.5 if the model could not discriminate the patients with and without events. Conversely, C-index was 1 if the probability predicted by the model was always higher for patients with events than those without events [12].

Calibration plot, the best method to visually exhibit the relationship between the predicted risk and the actual risk, was adopted in this study [12]. Calibration plots fall on a 45-degree diagonal line, reflecting excellent absolute risk estimates. NRI and IDI were usually used to assess and quantify the improvement in risk prediction between the new and old models [13]. The NRI was based on reclassification tables separately composed of patients with and without events and could quantify the correct reclassification in categories. The NRI could be calculated by adding the percentage of patients with events who were correctly reclassified to the percentage of patients without events who were correctly reclassified [12]. The IDI could reflect the improvement of sensitivity and specificity, and it also could be viewed as an integrated difference in Youden’s indices [13]. Calculating the IDI required adding the increased probability predicted by the new model compared to the old model for patients with events to the decreased probability predicted by the new model compared to the old model for patients without events [13]. NRI and IDI were both employed to compare the discriminative ability between the new model and the AJCC staging system in the current study.

Unlike the sensitivity, specificity, and area under the curve, DCA could be regarded as a method to directly compare benefits and harms which were put on the same scale. DCA plot could represent the model with the greatest net benefits had the highest clinical use, and it was widely used to estimate whether clinical use of diagnostic tests and prediction models would do more good than harm [14]. Therefore, DCA was conducted to evaluate the clinical use of the nomogram through quantifying the net benefit in comparison with the AJCC staging system in the training and validation sets.
All statistical tests were performed using R software (version 3.5.2, http://www.r-project.org/). All tests were two-sided, and the significance level was set at \( P < 0.05 \).

Results
Patient baseline characteristics
Between 2010 and 2016, 2315 metastatic RCC patients were identified from the SEER database based on inclusion criteria. The eligible patients were randomly separated into two sets at a ratio of 1:1, 1158 patients in the training set and 1157 patients in the validation set, respectively. Of all the patients, the median age was 61 (54–68), and the white race (83.8%) was the dominant race. Among the eligible patients, 1629 (70.4%) were males and 1559 (67.3%) were married. The most common histologic subtype was clear cell renal cell carcinoma (84.6%), and the most common Fuhrman grade was Grade III (40.0%). In terms of tumor stage, the majority of tumors were T3 (56.8%), followed by T2 (16.5%) and T4 (12.7%). With respect to treatment, 56.2% of the patients received chemotherapy, 23.3% of the patients received radiotherapy, and 85.6% of the patients underwent cancer-directed surgery. For metastasis, 31.5%, 9.9%, 11.0%, and 61.7% of the patients presented bone, brain, liver, and lung metastasis at diagnosis, respectively.

For the entire cohort, the median follow-up time was 43 months (95% CI, 41–44 months), and the median OS time was 19 months (95% CI, 18–21 months). By the end of the survey, 806 (69.6%) patients in the training set had died, among which 756 (93.8%) died from RCC and 50 (6.2%) died from other causes. The median follow-up time of the training set was 42 months (95% CI, 40–45 months), and the median survival time was 18 months (95% CI, 16–20 months). The demographic and clinical characteristics were summarized in Table 1.
**Table 1**

Patient demographics and clinical characteristics.

| Variables                     | All patients (n = 2315) | Training set (n = 1158) | Validation set (n = 1157) |
|-------------------------------|-------------------------|-------------------------|----------------------------|
| No. (%)                       |                         | No. (%)                 | No. (%)                    |
| Age, year                     | 61 (54–68)              | 60 (54–68)              | 61 (54–68)                 |
| Race                          |                         |                         |                            |
| White                         | 1941 (83.8%)            | 968 (83.6%)             | 973 (84.1%)                |
| Black                         | 174 (7.5%)              | 92 (7.9%)               | 82 (7.1%)                  |
| Other                         | 200 (8.6%)              | 98 (8.5%)               | 102 (8.8%)                 |
| Sex                           |                         |                         |                            |
| Male                          | 1629 (70.4%)            | 812 (70.1%)             | 817 (70.6%)                |
| Female                        | 686 (29.6%)             | 346 (29.9%)             | 340 (29.4%)                |
| Marital status                |                         |                         |                            |
| Married                       | 1559 (67.3%)            | 777 (67.1%)             | 782 (67.6%)                |
| Unmarried                     | 756 (32.7%)             | 381 (32.9%)             | 375 (32.4%)                |
| Histologic subtype            |                         |                         |                            |
| CCRCC                         | 1959 (84.6%)            | 982 (84.8%)             | 977 (84.4%)                |
| PRCC                          | 142 (6.1%)              | 56 (4.8%)               | 86 (7.4%)                  |
| CHRCC                         | 27 (1.2%)               | 14 (1.2%)               | 13 (1.1%)                  |
| SRCCT                         | 168 (7.3%)              | 91 (7.9%)               | 77 (6.7%)                  |
| CDRCC                         | 19 (0.8%)               | 15 (1.3%)               | 4 (0.3%)                   |
| Fuhrman grade                 |                         |                         |                            |
| Grade I                       | 57 (2.5%)               | 26 (2.2%)               | 31 (2.7%)                  |
| Grade II                      | 516 (22.3%)             | 247 (21.3%)             | 269 (23.2%)                |
| Grade III                     | 926 (40.0%)             | 482 (41.6%)             | 444 (38.4%)                |
| Grade IV                      | 816 (35.2%)             | 403 (34.8%)             | 413 (35.7%)                |
| Tumor size, mm                | 90 (70–118)             | 90.5 (70–120)           | 90 (68–115)                |
| Tumor classification          |                         |                         |                            |
| T1                            | 289 (12.5%)             | 141 (12.2%)             | 148 (12.8%)                |
| T2                            | 383 (16.5%)             | 198 (17.1%)             | 185 (16.0%)                |
| T3                            | 1316 (56.8%)            | 661 (57.1%)             | 655 (56.6%)                |
| T4                            | 293 (12.7%)             | 143 (12.3%)             | 150 (13.0%)                |
| TX                            | 34 (1.5%)               | 15 (1.3%)               | 19 (1.6%)                  |
| Lymph node status             |                         |                         |                            |
| N0                            | 1618 (69.9%)            | 796 (68.7%)             | 822 (71.0%)                |
| N1                            | 597 (25.8%)             | 310 (26.8%)             | 287 (24.8%)                |
| NX                            | 100 (4.3%)              | 52 (4.5%)               | 48 (4.1%)                  |
| Sarcomatoid feature           |                         |                         |                            |
| Yes                           | 446 (19.3%)             | 220 (19.0%)             | 226 (19.5%)                |
| No                            | 1697 (73.3%)            | 848 (73.2%)             | 849 (73.4%)                |
| Unknown                       | 172 (7.4%)              | 90 (7.8%)               | 82 (7.1%)                  |
| Chemotherapy                  |                         |                         |                            |
| Yes                           | 1302 (56.2%)            | 643 (55.5%)             | 659 (57.0%)                |
| No/Unknown                    | 1013 (43.8%)            | 515 (44.5%)             | 498 (43.0%)                |
| Radiotherapy                  |                         |                         |                            |
| Yes                           | 539 (23.3%)             | 255 (22.0%)             | 284 (24.5%)                |
| No                            | 1776 (76.7%)            | 903 (78.0%)             | 873 (75.5%)                |
| Cancer-directed surgery       |                         |                         |                            |
| Yes                           | 1982 (85.6%)            | 980 (84.6%)             | 1002 (86.6%)               |
| No                            | 333 (14.4%)             | 178 (15.4%)             | 155 (13.4%)                |
| Bone metastasis               |                         |                         |                            |
| Yes                           | 729 (31.5%)             | 361 (31.2%)             | 368 (31.8%)                |
| No                            | 1586 (68.5%)            | 797 (68.8%)             | 789 (68.2%)                |
| Brain metastasis              |                         |                         |                            |
| Yes                           | 230 (9.9%)              | 112 (9.7%)              | 118 (10.2%)                |
| No                            | 2085 (90.1%)            | 1046 (90.3%)            | 1039 (89.8%)               |
| Liver metastasis              |                         |                         |                            |
| Yes                           | 254 (11.0%)             | 126 (10.9%)             | 128 (11.1%)                |
| No                            | 2061 (89.0%)            | 1032 (89.1%)            | 1029 (88.9%)               |
| Lung metastasis               |                         |                         |                            |
| Yes                           | 1429 (61.7%)            | 723 (62.4%)             | 706 (61.0%)                |
| No                            | 886 (38.3%)             | 435 (37.6%)             | 451 (39.0%)                |
| Follow-up, month              |                         |                         |                            |
| Median (95%CI)                | 43 (41–44)              | 42 (40–45)              | 43 (40–46)                 |

**Independent Prognostic Factors**

Univariate and multivariate Cox regression analysis was carried out to find out independent risk factors.
factors of OS. Crude and adjusted HRs were presented in Table 2. After adjusting other risk factors, the results of multivariate Cox regression analysis showed that eight variables were significantly associated with OS, including Fuhrman grade, lymph node status, sarcomatoid feature, cancer-directed surgery, bone metastasis, brain metastasis, liver metastasis, and lung metastasis.
Table 2
Univariate and multivariate Cox regression analysis of OS in the training set.

| Variables                      | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | HR (95% CI)         | P         | HR (95% CI)         | P         |
| Age                            | 1.01 (1.00-1.02)    | 0.025     |                      |           |
| Race                           | Ref.                |           | Ref.                |           |
| White                          | Ref.                |           | Ref.                |           |
| Black                          | 1.26 (0.99-1.61)    | 0.06      | 1.18 (0.88-1.57)    | 0.223     |
| Other                          | 1.08 (0.84-1.38)    | 0.561     | 1.07 (0.91-1.26)    | 0.531     |
| Sex                            | Ref.                |           | Ref.                |           |
| Male                           | Ref.                |           | Ref.                |           |
| Female                         | 1.07 (0.92-1.24)    | 0.383     |                      |           |
| Marital status                 | Ref.                |           | Ref.                |           |
| Married                        | Ref.                |           | Ref.                |           |
| Unmarried                      | 1.12 (0.97-1.30)    | 0.117     |                      |           |
| Histologic subtypea            | Ref.                |           | Ref.                |           |
| CCRCC                          | Ref.                |           | Ref.                |           |
| PRCC                           | 1.28 (0.95-1.74)    | 0.106     |                      |           |
| CHRCC                          | 1.06 (0.55-2.04)    | 0.874     |                      |           |
| SRCC                           | 2.25 (1.78-2.85)    | < 0.001   | 2.42 (1.99-2.93)    | < 0.001   |
| CDRCC                          | 2.37 (1.40-4.03)    | 0.001     |                      |           |
| Fuhrman grade                  | Ref.                |           | Ref.                |           |
| Grade I                        | Ref.                |           | Ref.                |           |
| Grade II                       | 0.81 (0.48-1.35)    | 0.411     | 1.07 (0.64-1.81)    | 0.792     |
| Grade III                      | 0.94 (0.57-1.55)    | 0.809     | 1.38 (0.82-2.31)    | 0.223     |
| Grade IV                       | 1.46 (0.88-2.41)    | 0.142     | 1.80 (1.06-3.06)    | 0.029     |
| Tumor size                     | 1.001 (1.000-1.002) | 0.002     |                      |           |
| Tumor classification           | Ref.                |           | Ref.                |           |
| T1                             | Ref.                |           | Ref.                |           |
| T2                             | 1.42 (1.08-1.87)    | 0.013     |                      |           |
| T3                             | 1.47 (1.16-1.86)    | 0.002     |                      |           |
| T4                             | 2.43 (1.83-3.23)    | < 0.001   |                      |           |
| TX                             | 5.63 (3.18-9.97)    | < 0.001   |                      |           |
| Lymph node status              | Ref.                |           | Ref.                |           |
| N0                             | Ref.                |           | Ref.                |           |
| N1                             | 1.87 (1.61-2.18)    | < 0.001   | 1.54 (1.31-1.80)    | < 0.001   |
| NX                             | 1.85 (1.35-2.53)    | < 0.001   | 1.59 (1.15-2.20)    | 0.005     |
| Sarcomatoid feature            | Ref.                |           | Ref.                |           |
| Yes                            | Ref.                |           | Ref.                |           |
| Unknown                        | 1.05 (0.80-1.38)    | 0.709     | 0.84 (0.61-1.15)    | 0.282     |
| Chemotherapy                   | Ref.                |           | Ref.                |           |
| Yes                            | Ref.                |           | Ref.                |           |
| Radiotherapy                   | 0.83 (0.72-0.96)    | 0.011     |                      |           |
| Yes                            | Ref.                |           | Ref.                |           |
| No/Cancer-directed surgery     | Ref.                |           | Ref.                |           |
| Cancer-directed surgery        | Ref.                |           | Ref.                |           |
| Bone metastasis                | Ref.                |           | Ref.                |           |
| Yes                            | Ref.                |           | Ref.                |           |
| No                             | 2.61 (2.19-3.12)    | < 0.001   | 2.37 (1.91-2.93)    | < 0.001   |
| Brain metastasis               | Ref.                |           | Ref.                |           |
| Yes                            | Ref.                |           | Ref.                |           |
| No                             | 0.80 (0.69-0.93)    | 0.003     | 0.68 (0.58-0.80)    | < 0.001   |
| Liver metastasis               | Ref.                |           | Ref.                |           |
| Yes                            | Ref.                |           | Ref.                |           |
| No                             | 0.54 (0.44-0.68)    | < 0.001   | 0.61 (0.49-0.77)    | < 0.001   |
| Lung metastasis                | Ref.                |           | Ref.                |           |
| Yes                            | Ref.                |           | Ref.                |           |
| No                             | 0.54 (0.44-0.66)    | < 0.001   | 0.66 (0.54-0.81)    | < 0.001   |
| Nomogram Construction          |                      |           |                      |           |

The nomogram for predicting 1-, 3-, and 5-year OS were constructed on the basis of the significant
prognostic factors, which were exhibited in Table 2. As shown in the nomogram (Fig. 2), cancer-directed surgery made the greatest contribution to prognosis, followed by Fuhrman grade, brain metastasis, and sarcomatoid feature. The variables including lymph node status, liver metastasis, and lung metastasis represented moderate impacts on OS. Bone metastasis had the least effect on OS.

An Example Of Using The Nomogram
An example of how to use the nomogram was presented in Fig. 2. A patient was diagnosed as metastatic RCC with Fuhrman grade IV, N1 stage, no sarcomatoid feature, and lung metastasis. He underwent a cancer-directed surgery. Therefore, he would have 68 points for Fuhrman grade IV, 50 points for N1 stage, 0 points for no sarcomatoid feature, 45 points for bone metastasis, and 0 points for cancer-directed surgery, totaling 163 points. The total points corresponded to a 1-year survival probability of 57%, a 3-year survival probability of 20%, and a 5-year survival probability of 8%.

Nomogram Performance
Discrimination and calibration were employed to evaluate the model performance via the training and validation sets. The C-indexes of the nomogram were 0.701 (95% CI, 0.682–0.720) in the training set and 0.675 (95% CI, 0.654–0.696) in the validation set. With respect to the AJCC staging system, the C-indexes were 0.612 (95% CI, 0.591–0.633) in the training set and 0.600 (95% CI, 0.578–0.622) in the validation set, significantly lower than those of the nomogram (\( P < 0.001 \)). Calibration plots of the nomogram (Fig. 3) revealed excellent consistency between the predicted survival and the actual survival in both sets. The NRI values for 1-, 3- and 5-year follow-up were 0.553 (95% CI: 0.385–0.678), 0.547 (95% CI: 0.380–0.706) and 0.458 (95% CI: 0.284–0.703) in the training set, respectively. For the validation set, the NRI values for 1-, 3- and 5-year follow-up were 0.448 (95% CI: 0.309-0.600), 0.452 (95% CI: 0.305–0.626) and 0.360 (95% CI: 0.186–0.572), respectively. In addition, the IDI values for 1-, 3- and 5-year follow-up were 0.081 (\( P < 0.001 \)), 0.083 (\( P < 0.001 \)), and 0.063 (\( P < 0.001 \)) in the training set and 0.051 (\( P < 0.001 \)), 0.056 (\( P < 0.001 \)), and 0.047 (\( P < 0.001 \)) in the validation set, respectively. These results all exhibited the established nomogram had a better predictive ability of OS in comparison with the AJCC staging system.

Clinical Use
DCA plots showed that our nomogram had greater net benefits in comparison with the AJCC staging
system in terms of predicting 1-, 3- and 5-year OS in the training and validation sets (Fig. 4), indicating its clinical usefulness and help to decision-making.

**Discussion**

As we know, the outcomes of metastatic RCC patients vary widely because of clinical and pathological heterogeneity [9]. Therefore, how to accurately predict the prognosis of this population remains a great challenge. IMDC model, as the most widely investigated prognostic model for metastatic RCC patients receiving targeted therapy, was composed of six clinical and laboratory factors [8]. This model could stratify patients into three risk groups with different median OS, which had been validated in metastatic RCC patients who received first-line [8], second-line [15], and third-line targeted therapy [16]. However, this model merely provided the median OS (the time from the initiation of targeted therapy to death) for metastatic RCC patients in the same risk group and was lack of the prediction ability for individuals. Our study was performed based on a multicenter cohort with a large number of patients from the SEER database and focused on the newly diagnosed metastatic RCC patients for whom the IMDC model might be unsuitable. Meanwhile, the predictive model proposed in this study, presenting in the form of a nomogram, could provide a more accurate prediction of OS (the time from diagnosis with metastatic RCC to death), which was one of the most concerned issues for the individuals.

The model in this study was composed of eight clinical factors which were all demonstrated to be associated with adverse outcomes. The presence of lymph node metastasis was proved to have a negative effect on survival with an HR of 1.54 compared with the absence of lymph node metastasis. Karakiewicz et al identified 2530 RCC patients treated with nephrectomy from five institutions and proposed a nomogram for survival prediction by using six independent predictors, including tumor stage, lymph node status, metastatic status, tumor size, Fuhrman grade, and symptom classification [17]. Concerning metastatic RCC, Pati et al reported that lymph node metastasis had a significant impact on progression-free and overall survival [18], which was in accordance with the results from the Cleveland Clinic [7]. Fuhrman grade, as the most widely accepted prognostic grading system, had been confirmed to be associated with survival not only for RCC patients with local symptoms but for
those with distant symptoms [17]. In our study, Fuhrman grade IV presented a worse OS compared with grade I after adjusting other clinical variables (HR = 1.80, 95% CI: 1.06–3.06, \( p = 0.029 \)). Sarcomatoid feature was demonstrated to be another predictor of short survival for metastatic RCC patients. In terms of IMDC model, considering a small percentage of patients with sarcomatoid features (<6%), this predictor was not involved, though it was associated with adverse oncologic outcomes [8]. However, nearly 20% of the patients in our cohort had sarcomatoid features, and the patients without sarcomatoid features had superior OS compared with those with sarcomatoid features (HR = 0.61, 95% CI: 0.50–0.75, \( p < 0.001 \)). Therefore, we included this predictor into our model. The result of multivariate analysis showed that cancer-directed surgery performed had a significant benefit on OS of metastatic RCC patients (unperformed vs. performed, HR = 2.37, 95% CI: 1.91–2.93, \( p < 0.001 \)). Moreover, it could be observed from Fig. 2 that cancer-directed surgery exerted the greatest effect on the prognosis. Lack of prior nephrectomy was proved to be a risk factor for OS in the initial edition of MSKCC model [19]. A study from Patil et al also reported that prior nephrectomy performed could provide progression-free survival benefit for metastatic RCC patients administered Sunitinib as first-line therapy [18]. An important finding from Heng et al revealed that in the era of targeted therapy, a better OS benefit (20.6 vs. 9.6 months, \( p < 0.001 \)) could be obtained for metastatic RCC patients who received cytoreductive nephrectomy than those who did not. The patients with an estimated survival < 12 months and those with four or five IMDC prognostic factors might not benefit from cytoreductive nephrectomy [20].

An epidemiologic study from the Nationwide Inpatient Sample showed that the most common metastatic site of metastatic RCC patients was the lung, accounting for 45.2%, followed by the bone and the liver, affecting 29.5% and 20.3% of metastatic RCC patients, respectively [21]. As shown in Table 1, 61.7%, 31.5%, 11.1%, and 9.9% of the patients in our cohort represented lung, bone, liver, and brain metastasis, respectively. These four clinical variables were all significantly associated with adverse survival, and our findings were consistent with the growing evidence that the presence of distant metastasis for RCC patients predicted worse clinical outcomes. In a phase III trial of 375 metastatic clear cell RCC patients who received sunitinib, the presence of lung and liver metastases
was significantly associated with poor progression-free survival [22]. Another study from 23 centers of Italy involving 281 metastatic RCC patients administered with third-line targeted therapy demonstrated that the presence of metastases at diagnosis and presence of liver metastases had adverse effects on survival [23]. In a retrospective study of over 2000 patients who received first-line targeted therapy, presence of either bone or liver metastasis were independent risk factors of shorter OS, and presence of both bone and liver metastasis predicted worse survival in comparison with other metastatic sites. The author also reported that addition of bone and liver metastasis could significantly increase the predictive performance of IMDC model [24].

Discrimination and calibration are both important properties to evaluate the performance of a predictive model. Discrimination stands for the ability of a model to differentiate those at higher risks with those at lower risks. Calibration is used to describe the extent of accordance between the predicted absolute risks and the observed risks [12]. In the current study, our nomogram exhibited acceptable discrimination and calibration. C-indexes of the nomogram were significantly higher than those of the traditional AJCC staging system in the training set (0.701 vs. 0.612, \( P < 0.001 \)) and validation set (0.675 vs. 0.600, \( P < 0.001 \)). It could be observed from Fig. 3 that the calibration plots of 1-, 3- and 5-year follow-up exhibited an excellent visual agreement between the predicted survival and the observed survival. The results of NRI and IDI values also indicated an enhanced discriminative ability compared with the AJCC staging system, and the DCA plots revealed the higher clinical use of our model.

To the best of our knowledge, this is the first study to establish a nomogram for metastatic RCC patients by using the SEER database and demonstrate superior predictive ability of our nomogram in comparison with the traditional AJCC staging system. However, some limitations still exist in the current study. First of all, the main drawback of our study is attributed to the retrospective nature. Though our cohort derives from the SEER program which is a large and multicenter database, the selection bias induced in the process of patient selection is inevitable. Second, some laboratory factors which are demonstrated to be predictors for survival are not involved in the nomogram for these variables are not collected in the SEER database. We have reasons to believe that the
performance of our model will furtherly improve if these variables are taken into account. Finally, the
nomogram is subjected to internal validation by using a cohort from the SEER database. A more
comprehensive validation is still needed to increase the reliability of this model.

Conclusions
In summary, a nomogram of survival prediction for the patients of newly diagnosed with metastatic
RCC was established, in which eight clinical factors were involved, including Fuhrman grade, lymph
node status, sarcomatoid feature, cancer-directed surgery, bone metastasis, brain metastasis, liver
metastasis, and lung metastasis. The nomogram presented superior predictive capability and higher
clinical use compared with the conventional AJCC staging system. We believe that this study could
help clinicians to better identify the risks of survival and provide effective patient counseling on
therapeutic choices.

Abbreviations
OS: overall survival; RCC: renal cell carcinoma; SEER: Surveillance, Epidemiology, and End Results; C-
index: Harrell’s concordance index; IDI: integrated discrimination improvement; NRI: net reclassification
improvement; DCA: decision curve analysis; AJCC: American Joint Committee on Cancer;
MSKCC: Memorial Sloan-Kettering Cancer Center; IMDC: International Metastatic RCC Database
Consortium; CCRCC: clear cell renal cell carcinoma; PRCC: papillary renal cell carcinoma;
CHRCC: chromophobe renal cell carcinoma; SRCC: sarcomatoid renal cell carcinoma; CDRCC: collecting
duct renal cell carcinoma; HR: hazard ratio.

Declarations
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Authors’ Contributions
WWZ and WWZ participated in study design. SY, KL, YD, QW, and QT were responsible for data
collection and analysis. WWZ was involved in drafting the manuscript. CL, QZ, and CG revised the
manuscript. All authors read and approved the final manuscript.

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Availability of data and materials.
The datasets generated and/or analysed during the current study are available in the SEER repository (http://www.seer.cancer.gov).

Ethic approval and consent to participate
Our study was exempted from institutional review board approval because of using the de-identified data in the SEER database.

Consent for publication
Not applicable.

Competing Interests
The authors declared that they have no competing interests.

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Figures

Flow diagram of patient selection.
Figure 1

Flow diagram of patient selection.
Figure 2

The nomogram for predicting 1-, 3-, and 5-year OS of patients with metastasis RCC (A) and an example of using the nomogram (B). Each category of the prognostic variables was assign a score on the Points scale. After summing up the score of each variable and locating the total score on the Total Points scale, a line was vertically drawn to the 1-, 3-, and 5-year survival probability scale and estimated survival probability at each time point could be obtained.
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The calibration curves for predicting 1-, 3-, and 5-year OS of patients with metastasis RCC in training set (A, B, C) and in validation set (D, E, F). The nomogram-predicted probability of OS was plotted on the x-axis, and actual OS was plotted on the y-axis. The calibration curves could visually represent the relationship between the predicted and actual absolute risk.
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DCA of the nomogram and the AJCC staging system in the training set (A, B, C) and validation set (D, E, F) for 1-, 3-, and 5-year survival, respectively. The horizontal coordinates represented the threshold probability, and the vertical coordinates represented the net benefit rate. The red dash line stood for the DCA of the nomogram, and the black dash line stood for the DCA of the AJCC staging system. The black solid line assumed all patients were alive, and the gray solid line with a negative slope assumed all patients were dead. DCA plot could represent the model with the highest net benefit had the highest clinical use.
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