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# Novel survival nomograms for patients with lung metastatic clear cell renal cell carcinoma

## A population-based study

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**Abstract**

Survival heterogeneity is observed among renal cell carcinoma (RCC) patients with metastases in different organs. Moreover, almost all previous prognostic nomograms based on data from metastatic RCC patients did not take competing events, such as death from cerebrovascular and heart diseases, into account. We aimed to construct novel prognostic nomograms for patients with lung metastatic clear cell RCC (LMCCRCC).

Data of 712 non-Hispanic white LMCCRCC patients registered in the Surveillance, Epidemiology, and End Results database were retrospectively analyzed. Nomograms for predicting overall survival (OS) and disease-specific survival (DSS) were established using the Cox approach and Fine and Gray approach, respectively, and their performances were assessed using the concordance index (C-index), calibration plots, and an independent cohort comprising 181 Hispanic patients.

Sex, tumor grade, T stage, N stage, presence or absence of bone metastases, and presence or absence of brain metastases were independent predictors for both OS and DSS. Additionally, presence or absence of liver metastases was an independent predictor only for DSS. Meanwhile, age at diagnosis was independently associated with OS. The C-indexes of the nomograms were 0.702 for OS and 0.723 for DSS in internal validation. In external validation, the C-indexes were 0.700 for OS and 0.708 for DSS. Both internal and external calibration plots showed excellent consistency between the prediction and the observation.

The current study developed a novel nomogram for predicting individual OS in LMCCRCC patients. Moreover, we constructed an effective competing risk nomogram for predicting their individual DSS for the first time.

**Abbreviations:** CI = confidence interval, CIF = cumulative incidence function, C-index = concordance index, DSS = disease-specific survival, HR = hazard ratio, LMCCRCC = lung metastatic clear cell renal cell carcinoma, mRCC = metastatic RCC, OS = overall survival, RCC = renal cell carcinoma, SEER = Surveillance, Epidemiology and End Results, sHR = subdistribution hazard ratio.

**Keywords:** lung metastases, nomogram, renal cell carcinoma, SEER, survival

## 1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of all cancer cases, with the worldwide incidence increasing by approximately 2% annually over the past 20 years.[1] In the USA, there were an expected 73,750 newly diagnosed cases in 2020, and approximately 14,830 patients died of RCC.[2] Approximately 30% of patients with RCC have metastases at initial diagnosis, with the lung accounting for 60% to 70% of all metastases.[3,4] As the predominant histological subtype, clear cell RCC (CCRCC) accounts for approximately 90% of all RCCs, and it is more likely to metastasize to the lung than other subtypes.[3,5]

The American Joint Committee on Cancer TNM staging system is the most commonly used system for RCC.[6] However, significant survival heterogeneity was observed in lung metastatic CCRCC (LMCCRCC) patients with the same TNM stage in clinical practice. Nomograms, which are graphical representations of multivariate models, always integrate more prognostic factors and are more accurate in predicting the survival of patients with certain malignancies than traditional staging systems.[7–10] In the past 2 decades, several prognostic nomograms have been developed for RCC patients,[1,11–18] and some of them were based only on data from metastatic RCC (mRCC) patients.[12–17] However, significant survival heterogeneity is

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LZ, GH, MG, and YZ contributed equally to this study.

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The datasets generated during and/or analyzed during the current study are publicly available.

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observed among mRCC patients with metastases in different organs; thus, previous nomograms based on data from mRCC patients may show low accuracy and low precision when they are used in LMCCRCC patients. Furthermore, almost all of these nomograms were developed using only the Cox approach, which can handle only 1 event and would reproduce unreliable results inevitably when competing events, such as death from cerebrovascular and heart diseases, exist. To date, a competing risk prognostic nomogram, which can be applied to LMCCRCC patients, has not been established yet.

Considering the reasons mentioned above, the current study aimed to investigate the independent predictors for overall survival (OS) and disease-specific survival (DSS) in LMCCRCC patients and to develop novel prognostic nomograms exclusive for these patients.

## 2. Materials and methods

### 2.1. Study design

The Surveillance, Epidemiology, and End Results (SEER) database supported by the National Cancer Institute encompasses data from 18 SEER registries and covers approximately 30% of the US population.[19,20] Data from 66,813 non-Hispanic

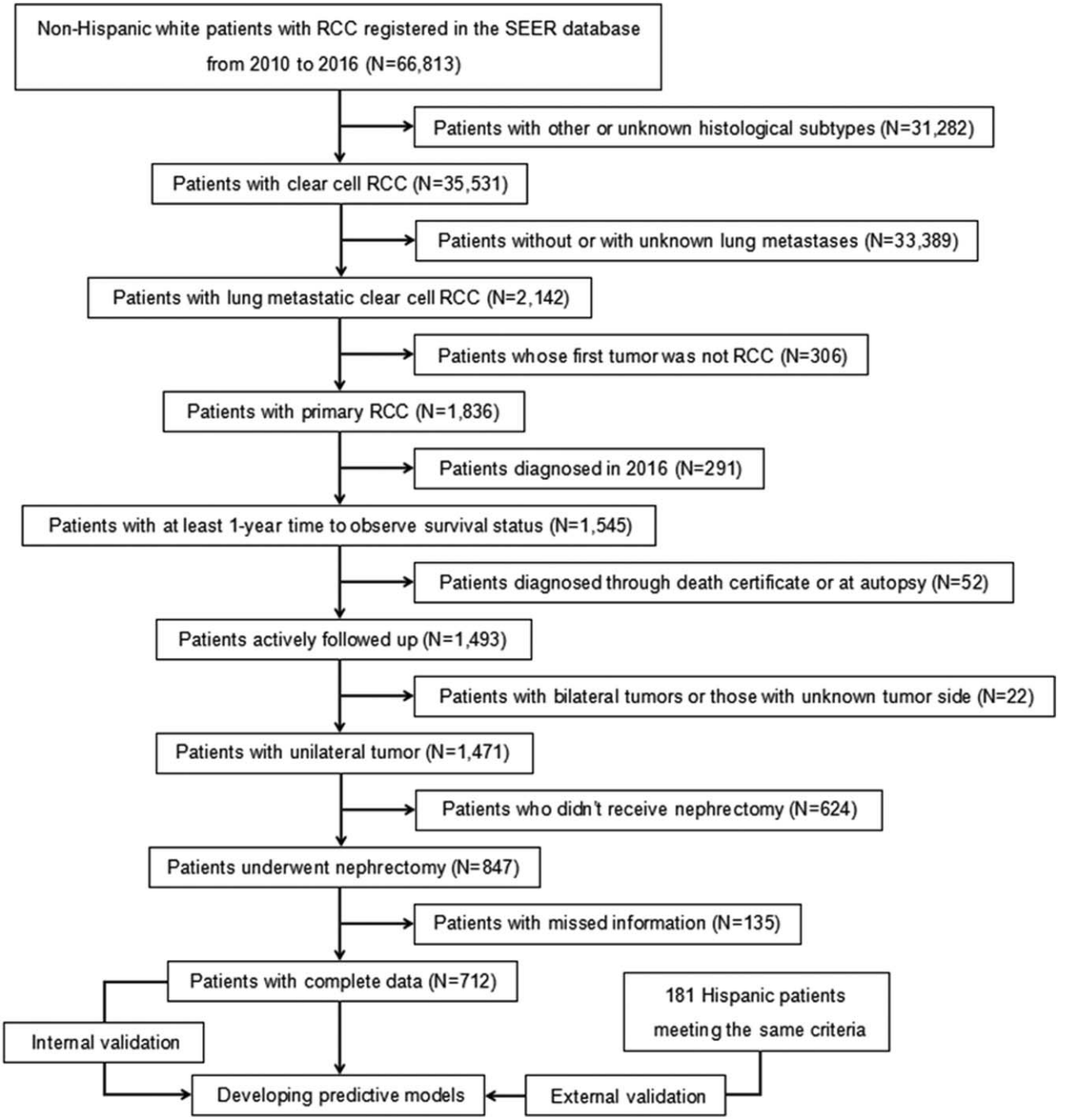


**Figure 1.** Flowchart of patient selection. RCC = renal cell carcinoma, SEER = Surveillance, Epidemiology and End Results.

**Table 1**

**Demographics and clinicopathologic characteristics of patients with lung metastatic clear cell renal cell carcinoma.**

| Characteristic | Training cohort (n = 712) | | Validation cohort (n = 181) | | *P* value |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Race | non-Hispanic white | | Hispanic | | |
| Age | | | | | .011 |
| Range | 30–91 | | 35–84 | | |
| Median | 61 | | 59 | | |
| Sex | | | | | .319 |
| Male | 515 | 72.3 | 124 | 68.5 | |
| Female | 197 | 27.7 | 57 | 31.5 | |
| Tumor side | | | | | .889 |
| Left | 366 | 51.4 | 92 | 50.8 | |
| Right | 346 | 48.6 | 89 | 49.2 | |
| Tumor size (cm) | | | | | .886 |
| Range | 1.0–30.0 | | 1.0–22.5 | | |
| Median | 10.0 | | 10.0 | | |
| Tumor grade | | | | | .029 |
| I | 4 | 0.6 | 4 | 2.2 | |
| II | 107 | 15.0 | 28 | 15.5 | |
| III | 295 | 41.4 | 89 | 49.2 | |
| IV | 306 | 43.0 | 60 | 33.1 | |
| T stage | | | | | .032 |
| T1 | 58 | 8.1 | 15 | 8.3 | |
| T2 | 77 | 10.8 | 29 | 16.0 | |
| T3 | 498 | 69.9 | 108 | 59.7 | |
| T4 | 79 | 11.1 | 29 | 16.0 | |
| N stage | | | | | .523 |
| N0 | 539 | 75.7 | 141 | 77.9 | |
| N1 | 173 | 24.3 | 40 | 22.1 | |
| With bone metastases | | | | | .712 |
| No | 587 | 82.4 | 147 | 81.2 | |
| Yes | 125 | 17.6 | 34 | 18.8 | |
| With brain metastases | | | | | .181 |
| No | 659 | 92.6 | 162 | 89.5 | |
| Yes | 53 | 7.4 | 19 | 10.5 | |
| With liver metastases | | | | | .372 |
| No | 646 | 90.7 | 168 | 92.8 | |
| Yes | 66 | 9.3 | 13 | 7.2 | |

white RCC patients registered from January 2010 to December 2016 were collected using SEER*Stat Software (version 8.3.5.) after obtaining approval for using the SEER database (username: 10646-Nov 2018).

The inclusion criteria were as follows:

1. patients with primary RCC,
2. patients with histological subtype CCRCC (codes 8310/3, according to the International Classification of Diseases for Oncology, Third Revision),
3. patients undergoing nephrectomy, and
4. patients with complete clinical or demographic data.

The exclusion criteria were as follows: patients

1. with other or unknown histological subtypes,
2. with unknown or without lung metastases,
3. diagnosed at autopsy or through death certificate only,
4. whose first carcinoma was not RCC,
5. with bilateral tumors, and
6. diagnosed after December 31, 2015.

Finally, a total of 839 non-Hispanic white patients were included, and they comprised the training cohort, which was used to develop the nomograms. Moreover, an independent cohort comprising 230 Hispanic patients was used to externally validate the performance of the non-Hispanic white patient-based nomograms. Of note, these Hispanic patients met the identical criteria as applied to those in the training cohort, and they were registered in the same database during the same period. The flowchart of patient selection is shown in Figure 1.

In the current study, OS was defined as the interval from initial diagnosis to death from any cause, whereas DSS was the interval from initial diagnosis to death due to RCC. Death due to other causes was defined as competing risks. The last unified follow-up was conducted at the end of December 2016. Since RCC is a reportable disease in every state of the USA and patient information is anonymized in the SEER database, ethical approval, and informed consent from patients were not required. Furthermore, the current study conformed to the 1964 Declaration of Helsinki and its relevant amendments.

### 2.2. Statistical analysis

All statistical analysis were performed using R software version 3.6.1 (http://www.r-project.org/) and the International Business

**Table 2**

**Cumulative incidence function analysis of death causes in patients with lung metastatic clear cell renal cell carcinoma in the training cohort.**

| | Overall death (%) | | | | Disease-specific death (%) | | | |
|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **1-year** | **2-year** | **3-year** | ***P* value** | **1-year** | **2-year** | **3-year** | ***P* value** |
| Age (years) | | | | .653 | | | | .426 |
| <60 | 32.7 | 49.3 | 64.9 | | 31.7 | 47.6 | 62.8 | |
| ≥60 | 29.8 | 52.0 | 62.9 | | 28.0 | 48.7 | 59.2 | |
| Sex | | | | .040 | | | | .023 |
| Male | 28.4 | 49.1 | 61.9 | | 27.0 | 46.2 | 58.6 | |
| Female | 38.2 | 55.1 | 70.0 | | 36.6 | 53.6 | 67.5 | |
| Tumor side | | | | .337 | | | | .224 |
| Left | 33.8 | 52.8 | 65.2 | | 32.4 | 50.8 | 62.7 | |
| Right | 28.3 | 48.7 | 62.8 | | 26.8 | 45.5 | 59.2 | |
| Tumor size (cm) | | | | .887 | | | | .470 |
| <10.0 | 29.5 | 51.1 | 66.3 | | 28.1 | 47.3 | 61.4 | |
| ≥10.0 | 32.6 | 50.5 | 62.2 | | 31.2 | 49.1 | 60.7 | |
| Tumor grade | | | | <.001 | | | | <.001 |
| I & II | 19.2 | 33.8 | 44.8 | | 16.5 | 29.1 | 40.0 | |
| III | 23.3 | 45.6 | 62.7 | | 21.3 | 42.3 | 58.5 | |
| IV | 43.1 | 62.4 | 72.6 | | 42.7 | 61.2 | 71.4 | |
| T stage | | | | <.001 | | | | <.001 |
| T1 | 15.7 | 25.8 | 45.8 | | 15.7 | 21.6 | 41.6 | |
| T2 | 20.8 | 44.9 | 56.1 | | 20.8 | 43.5 | 53.1 | |
| T3 | 32.0 | 52.5 | 65.6 | | 30.0 | 49.6 | 62.3 | |
| T4 | 47.7 | 64.9 | 76.4 | | 47.7 | 64.9 | 76.4 | |
| N stage | | | | <.001 | | | | <.001 |
| N0 | 24.7 | 44.8 | 59.4 | | 23.4 | 42.0 | 56.0 | |
| N1 | 51.2 | 69.8 | 78.5 | | 49.4 | 68.0 | 76.7 | |
| With bone metastases | | | | <.001 | | | | <.001 |
| No | 28.5 | 47.6 | 61.6 | | 27.3 | 45.2 | 58.7 | |
| Yes | 43.3 | 66.1 | 75.6 | | 40.8 | 62.6 | 72.1 | |
| With brain metastases | | | | .001 | | | | <.001 |
| No | 29.1 | 49.1 | 63.0 | | 27.6 | 46.2 | 59.7 | |
| Yes | 55.8 | 72.8 | 76.2 | | 55.8 | 72.8 | 76.2 | |
| With liver metastases | | | | .064 | | | | .016 |
| No | 29.8 | 49.8 | 63.0 | | 28.2 | 46.9 | 59.7 | |
| Yes | 43.9 | 60.3 | 73.5 | | 43.9 | 60.3 | 73.5 | |

Machines Corporation (IBM) Statistical Package for the Social Sciences Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Categorical data are presented as "frequencies (proportions)" and compared using the Chi-Squared test. Continuous variables are presented as "medians (ranges)" and compared using the Mann–Whitney *U* test. The cumulative incidence function (CIF) based on the competing risk model was used to describe the probability of death, and Gray test was performed to test between-group differences in CIF values. The variable age at diagnosis and tumor size were grouped as categorical variables, according to the median, for calculating CIF of mortality.

The independent predictors for OS and DSS were identified by multivariate analyses based on the Cox approach and Fine and Gray approach, respectively. Variables achieving statistical significance in the multivariate analyses were entered into the final models. The discriminatory performance, namely, the predictive accuracy, of the nomograms was measured using the Harrell concordance index (C-index),[21] with a C-index of 1 representing perfect discriminatory performance and a C-index of 0.5 indicating agreement by chance. Furthermore, calibration plots were generated for the nomograms to test the agreements between the nomogram-predicted and actual survival, with predictions being expected to fall on the diagonal line in perfect calibrated nomograms. To reduce the overfit bias, bootstrapping with 1000 resamples was performed for these calculations.

Differences with two-tailed $P < .05$ were considered statistically significant.

## 3. Results

### 3.1. Characteristics of patients and survival outcomes

The demographic and clinicopathological characteristics of the training and validation cohorts are listed in Table 1.

In total, 441 of the 712 patients died from RCC, whereas 22 patients died of other causes during follow-up, with a median follow-up of 31 months (interquartile range, 20–49) for patients who were alive at the last follow-up. The cumulative incidence rates of the 1-year, 2-year, and 3-year overall death were 31.1%, 50.8%, and 64.1%, respectively, and the cumulative incidence rates of the 1-year, 2-year, and 3-year disease-specific death were 29.7%, 48.2%, and 61.0%, respectively.

**Table 3**

**Final hazard models of probabilities of death for patients with lung metastatic clear cell renal cell carcinoma in the training cohort.**

| Characteristic | Death from any cause* | | | Disease-specific death† | | |
|---|---|---|---|---|---|---|
| | Coefficient | HR (95% CI) | *P* value | Coefficient | sHR (95% CI) | *P* value |
| Age | 0.011 | 1.011 (1.002–1.021) | .021 | – | – | – |
| Female | 0.299 | 1.349 (1.098–1.658) | .004 | 0.318 | 1.375 (1.110–1.703) | .035 |
| Tumor grade | | | | | | |
| III | 0.182 | 1.199 (0.890–1.616) | .233 | 0.222 | 1.248 (0.910–1.713) | .169 |
| IV | 0.534 | 1.706 (1.262–2.307) | .001 | 0.625 | 1.868 (1.361–2.562) | <.001 |
| T stage | | | | | | |
| T2 | 0.441 | 1.554 (0.954–2.532) | .077 | 0.410 | 1.507 (0.910–2.496) | .111 |
| T3 | 0.603 | 1.828 (1.205–2.772) | .005 | 0.558 | 1.747 (1.132–2.695) | .012 |
| T4 | 0.697 | 2.008 (1.225–3.293) | .006 | 0.594 | 1.811 (1.079–3.041) | .025 |
| N1 stage | 0.523 | 1.687 (1.370–2.078) | <.001 | 0.544 | 1.722 (1.389–2.135) | <.001 |
| With bone metastases | 0.476 | 1.610 (1.285–2.017) | <.001 | 0.422 | 1.524 (1.206–1.927) | <.001 |
| With brain metastases | 0.443 | 1.557 (1.118–2.169) | <.001 | 0.509 | 1.664 (1.189–2.328) | .003 |
| With liver metastases | – | – | – | 0.304 | 1.355 (1.002–1.849) | .049 |

* Based on the Cox proportional hazards model.

† Based on the Fine and Gray proportional subdistribution hazard model.

The cumulative incidences of deaths according to the clinicopathological characteristics are listed in Table 2.

### 3.2. Independent prognostic factors for OS and DSS

Sex, tumor grade, T stage, N stage, presence or absence of bone metastases, and presence or absence of brain metastases were independent predictors for both OS and DSS. Additionally, presence or absence of liver metastases was an independent predictor only for DSS. Meanwhile, age at diagnosis was independently associated with OS (Table 3).

### 3.3. Construction and validation of the nomograms

Nomograms for predicting individual OS and DSS were constructed by integrating independent predictors (Fig. 2). In both nomograms, T3 and T4 stage and grade IV and N1 stage made substantial contributions to an inferior prognosis.

The C-indexes of the nomograms were 0.702 (95% confidence interval [CI], 0.679–0.725) for OS and 0.723 (95% CI, 0.713–0.733) for DSS in internal validation. In external validation, the C-indexes were 0.700 (95% CI, 0.655–0.745) for OS and 0.708 (95% CI, 0.681–0.735) for DSS. Excellent agreements were observed between nomogram predictions and actual observations in both internal and external calibration plot diagrams (Fig. 3).

## 4. Discussion

Although lung metastasis is not an independent risk factor for the prognosis of RCC patients, it affects patient survival to some extent even if a substantial number of patients with multiple metastases were included.[14,22] In particular, lung metastasis is still an independent risk factor of OS in patients with RCC when bone metastasis exists.[23] Currently, data on the prognostic factors in LMCCRCC patients are insufficient. Moreover, previous prognostic models based on data from mRCC patients may show low accuracy and low precision when they are used in

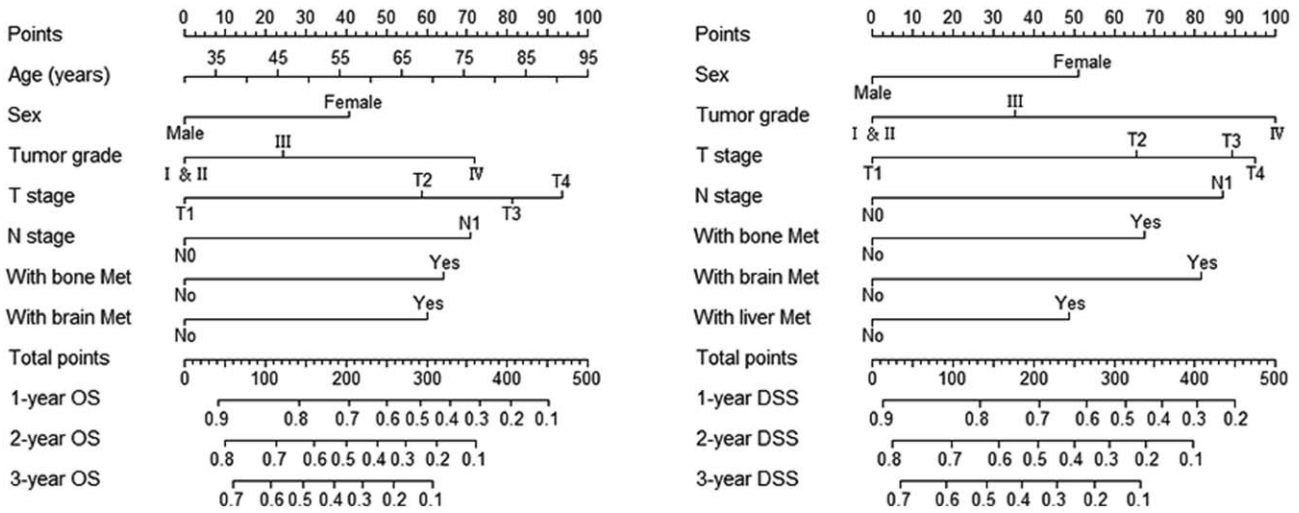


Figure 2. Nomograms predicting overall survival and disease-specific survival of patients with lung metastatic clear cell renal cell carcinoma.

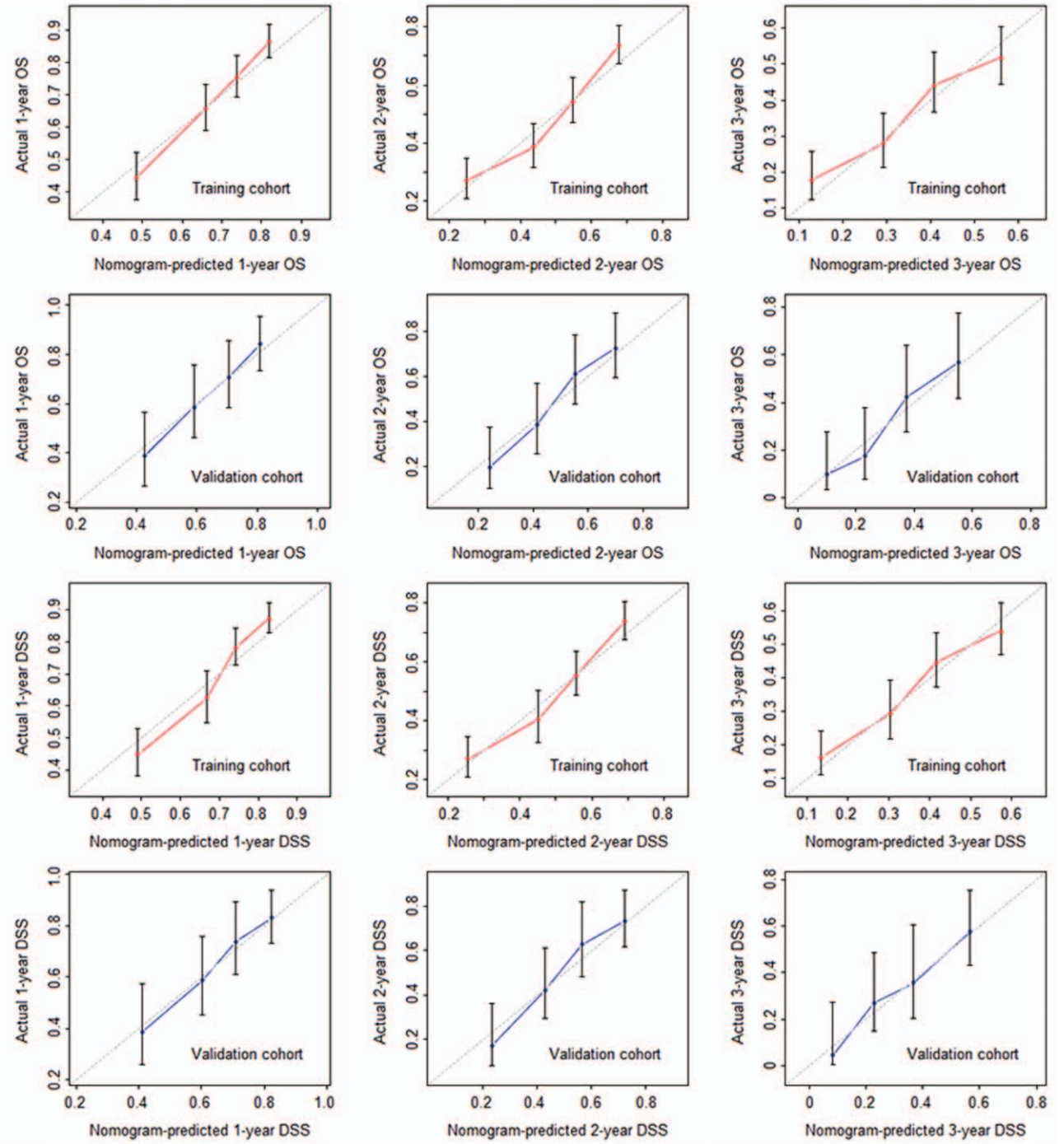


**Figure 3.** Calibration plots for predicting 1-, 2-, and 3-year overall and disease-specific survival. The nomogram-predicted and actual survival are plotted on the x- and y-axes, respectively. The imaginary line indicates a perfect calibration model in which the predicted probabilities are identical to the actual survival outcomes.

LMCCRCC patients because significant survival heterogeneity is observed among mRCC patients with metastases in different organs. Furthermore, almost all of these models did not take competing events into consideration. Therefore, the current study aimed to investigate the independent predictors for OS and DSS in LMCCRCC patients and to develop novel prognostic nomograms exclusive for these patients.

In the current study, we observed 1.524-, 1.664-, and 1.355-fold risks of disease-specific death for patients with additional bone, brain, and liver metastases, respectively, compared to RCC patients with metastases only in the lung, a finding consistent with the findings reported by Negrier and colleagues,[24] who identified the number of metastatic sites as an independent prognostic factor for mRCC patients. Therefore, we recommend that RCC patients undergo a whole-body bone scan regardless of alkaline phosphatase level and head magnetic resonance imaging regardless of neurological symptoms immediately after lung metastases are found to

determine whether bone and brain metastases have occurred, to more accurately confirm the disease severity, and to provide more reasonable treatments. Of note, although liver metastases was an independent risk predictor for DSS in LMCCRCC patients, it is not an independent predictor for OS, and the predictive accuracy of the nomogram predicting OS would increase only by approximately 0.009 when we add this variable into this nomogram.

In previous studies based on data of mRCC patients, no significant difference in OS was observed between the older and younger age groups.[12,25] Interestingly, age was identified as an independent predictor for OS when mRCC patients were restricted to those with LMCCRCC, similar to the finding in patients with bone mRCC,[23] which may be attributed to a decline in immune system function and changes in tumor behavior. Another novel finding of our study was that female sex was an independent risk predictor for both OS and DSS in LMCCRCC patients, and this finding was inconsistent with the findings of previous studies based on data of mRCC patients, where sex was not considered as a predictor for survival.[12,14] Although the mechanism by which women have worse outcomes is unknown, it may be reasonable for female LMCCRCC patients to be followed up more carefully because female LMCCRCC patients have a higher (1.375-fold) risk of disease-specific death compared to male patients according to the results of multivariate analysis in our study. Findings above indicated that several variables are independent prognostic predictors in LMCCRCC patients, but not in all mRCC patients. Hence, it is necessary to develop exclusive prognostic nomograms for LMCCRCC patients.

Conclusions from a population-based study are more likely to be generalizable compared with those from single-institute studies, which are potentially subject to selection bias. Hence, our study population would be a good representation of the general non-Hispanic white LMCCRCC patients. Moreover, all variables contributing to the nomograms are easy to obtain in clinical practice, which ensures the convenience of using the nomograms. Furthermore, in the external validation using a Hispanic dataset, C-indexes of 0.700 for OS and 0.708 for DSS were produced and excellent agreements between nomogram prediction and the actual observation were reached, which indicated the broad applicability of our nomograms to a large extent.

The current study has several limitations that should be considered. First, we did not analyze the Charlson Comorbidity Index, targeted therapy, and pulmonary metastasectomy, which may also have significant impacts on the OS and DSS in LMCCRCC patients, because these variables were not available from the SEER database. Second, no comparison in predictive accuracy was conducted between our nomogram predicting OS and the International Metastatic Renal Cancer Database Consortium (IMDC) risk model[12] considering that the variables contributing to the IMDC risk model were not registered in the SEER database. Third, patients with missing data for any of the variables were excluded from our cohort, which may have increased the selection bias. Finally, we did not externally validated the nomograms using data of Asian and African–American patients because the small number of these patients met the inclusion criteria of our study. Despite these limitations, good discrimination and calibration of our nomograms can still be guaranteed when they are used in non-Hispanic white and Hispanic patients with LMCCRCC.

## 5. Conclusion

In the current study, independent predictors for OS and DSS were identified and probabilities of survival were measured in LMCCRCC patients. Furthermore, a novel nomogram predicting individual OS and an effective competing risk nomogram predicting individual DSS were developed exclusive for these patients. With good discrimination and calibration, our individualized predictive tool will be useful for patient counseling and clinical trial designing in non-Hispanic white and Hispanic patients with LMCCRCC. Validations using data of Asian and African–American patients are required to test the broader applicability of our nomograms.

## Author contributions

**Analysis and interpretation of data:** Yu Zheng, Lei Zhang, Fuli Wang, and Guangdong Hou.
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**Writing – review & editing:** Ming Gao, Fei Yan, Ping Meng, Jiarui Yuan.

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