Observational Study

Medicine

OPEN

Nomogram to predict risk and prognosis of synchronous lung metastasis in renal cell carcinoma

A large cohort analysis

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Abstract

We aimed to construct and validate nomogram models that predict the incidence of lung metastasis (LM) in patients with renal cell carcinoma (RCC) and evaluate overall survival (OS) and cancer-specific survival (CSS) among RCC patients with LM.

The Surveillance, Epidemiology, and End Results database was analyzed for RCC patients diagnosed between 2010 and 2015. The X-tile program was used to determine the best cutoff values for age at initial diagnosis and tumor size. Logistic regression analysis was performed to explore independent risk factors for LM, and COX regression analysis was used to identify prognostic indicators for OS and CSS in lung metastatic RCC patients. Subsequently, 3 nomograms were established, and receiver operating characteristic (ROC) curves and decision curve analysis (DCA) were utilized to validate their accuracy.

We randomly assigned 10,929 patients with RCC to 2 groups with 1:1 allocation. Multivariate logistic analyses revealed that pathology, tumor (T) stage, nodes (N) stage, race, grade, surgery, metastatic sites, and tumor size were independent risk factors for LM. Multivariate Cox analyses showed that pathology, T stage, N stage, age, surgery, metastatic sites, and residence were independent prognostic factors for OS and CSS in patients with LM. Then, nomograms were developed based on the multivariate logistic and Cox regression analyses results. The ROC and DCA curves confirmed that these nomograms achieved satisfactory discriminative power.

Three effective nomograms were constructed and validated that can be used to assist clinicians in predicting the incidence of LM and evaluating the prognosis of lung metastatic RCC.

Abbreviations: AJCC = American Joint Committee on Cancer, AUC = area under curve, CSS = cancer-specific survival, DCA = decision curve analysis, LM = lung metastasis, MRCC = metastatic renal cell carcinoma,OS = overall survival,RCC = renal cell carcinoma, ROC = receiver operating characteristics, SEER = Surveillance, Epidemiology, and End Results, TNM = tumor, nodes, metastases.

Keywords: carcinoma, nomograms, renal cell, SEER program

1. Introduction

According to statistics from 2020, renal cell carcinoma (RCC) accounted for 80% to 85% of renal malignant tumors and 2% to 3% of systemic malignancies, which may be partially attributed to widely available cross-sectional imaging in the last 2 decades.[1] Approximately 30% of patients with RCC were initially diagnosed with advanced RCC, and approximately 16% of patients presented with metastatic renal cell carcinoma (MRCC) at the initial visit.[2,3]

To our knowledge, RCC with distant metastasis is significantly associated with a poor prognosis. In patients with RCC, synchronous lung metastasis (LM) is the most common, followed by bone, liver, and brain metastases.[4] In recent years, few prognostic nomograms have been constructed for MRCC, and many are based solely on the American Joint Committee on Cancer (AJCC) or TNM (tumor, nodes, metastases) staging systems and demonstrate low prediction accuracy. Therefore, several combination models were developed to predict the rate of LM and assess the prognosis of RCC patients with LM.

ZL and CY contributed equally to the manuscript.

The authors have no funding and conflicts of interest to disclose.

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

Ethics statement: The authors certify that each author participated sufficiently in this study and they have approved the final version of the manuscript. The study was managed in accordance with WMA "The declaration of Helsinki" and CIOMS "International ethical guidelines for biomedical research involving."

Supplemental Digital Content is available for this article.

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How to cite this article : Lu Z, Yang C, He W, Zhou J, Xiang R. Nomogram to predict risk and prognosis of synchronous lung metastasis in renal cell carcinoma: A large cohort analysis. Medicine 2022;101:27(e29764).

Received: 18 November 2021 / Received in final form: 10 May 2022 / Accepted: 23 May 2022

http://dx.doi.org/10.1097/MD.0000000000029764

In the current study, we identified independent risk predictors for lung MRCC patients using logistic regression model analyses and created a prediction model that allows clinicians to predict LM risk. In addition, we identified independent prognostic factors for RCC patients with LM and developed nomograms to predict overall survival (OS) and cancer-specific survival (CSS). Then, we validated the prediction accuracy of the nomograms using receiver operating characteristic (ROC) curves and decision curve analysis (DCA).

2. Methods

2.1. Patients and variables

The clinicopathological parameters and prognoses were obtained from the Surveillance, Epidemiology, and End Results (SEER) database (username: 14622-Nov2017), which contains 18 cancer registries and includes approximately 30% of the US population.[5,6]

In the present study, we included patients who were initially diagnosed with RCC and only primary tumors. The inclusion criteria were as follows: age at diagnosis, tumor size, lymphadenectomy scope, tumor (T) stage, nodes (N) stage, sex, race, laterality, grade, median household income, residential area, surgery, metastatic sites, and histological type (histological codes: 8310/3, 8313/3, 8260/3, 8317/3, 8270/3, and 8319/3). The exclusion criteria were as follows: unknown TNM stage, treatment options, metastatic information, tumor size or side, survival months, or status. Ultimately, a total of 10,929 patients with RCC were identified from 2010 to 2015 and randomly divided into a training cohort (n = 601) and a validation group (n = 600) at a ratio of 1:1. The training cohort was used to develop a nomogram for predicting the incidence of LM, which was verified in the validation group (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G809). Finally, 513 RCC patients with LM were selected from the SEER database and the probabilities of 1-, 3-, and 5-year OS and CSS were assessed.

2.2. Follow-Up

The final follow-up was conducted in December 2015. OS and CSS were the primary outcomes of this study. OS was managed from the time of the initial diagnosis to death from all causes or to the last follow-up visit when the patient was still alive.[7] CSS was analyzed from the date of initial diagnosis to death from lung MRCC or to the last visit when the patient was still alive.[8]

2.3. Statistical analysis

The categorical variables were summarized as percentages and calculated using the chi-squared test. The X-tile program[9] (Yale University, New Haven, CT, USA) was used to define the best cutoff values for age at initial diagnosis and tumor size. Tumor size was trivially stratified (<76, 76–96, and >96 mm), and age was stratified into 3 levels (<55, 55–73, and >73 years; Figure S2, Supplemental Digital Content, http://links.lww.com/MD/G809.

In the training cohort, univariate and multivariate logistic analyses were performed to identify LM-associated independent risk factors in RCC patients. The logistic risk model was constructed with the "glm" package in R software to quantify the relationship between LM and the risk factors, and played a significant role in personal diagnostic prediction. Meanwhile, a ROC curve was applied to identify the discriminatory performance of the predictive nomogram, which was also compared with the discriminative ability of each significant risk factor in the training cohort and validation group. Variables in the univariate Cox analysis with P values <.1 were included in the multivariate analysis to determine the independent predictors for OS and CSS. Two prognostic nomograms of OS and CSS were developed using the "rms" and "survival" packages in R software. The predictive accuracy and clinical value of the 2 nomograms were evaluated using ROC and DCA, respectively.

All statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY) and R version 4.1.0 software (R Foundation for Statistical Computing, Vienna, Austria); a 2-tailed P value <.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The clinicopathological characteristics of the study population are summarized in Table 1. A total of 10,929 eligible patients were selected from the SEER database and randomized in a 1:1 ratio into 2 groups: 5465 cases in the training cohort and 5464 cases in the validation group. No significant differences were found in tumor size, lymphadenectomy scope, T stage, N stage, sex, race, laterality, grade, median household income, residential area, surgery, and metastatic sites. The histological type and age at diagnosis were similar between the 2 groups.

3.2. LM risk nomogram construction and validation

Univariate and multivariate logistic regression analyses were performed to identify the LM-associated factors in the developing cohort (Table 2). Race; histological type; T stage; grade; N stage; surgery; lymphadenectomy scope; tumor size; residence; and bone, liver, and brain metastases were significant risk factors in the univariate analysis for LM. After comprehensive analysis using the multivariate logistic model, histologic type; T stage; grade; N stage; surgery; race; tumor size; and bone, liver, and brain metastases remained independent risk factors for LM ($P < .05$).

Based on the results of the multivariate logistic regression analysis, we constructed a probability nomogram to predict the incidence of LM in RCC patients (Fig. 1). In this predictive nomogram, the total score of each individual patient was obtained by calculating the corresponding scores of various categories of each independent predictor. The corresponding total points scale represents the probability of LM for each patient. We evaluated and validated the accuracy of this model using ROC curves, which are shown in Figure 2. The area under the curve (AUC) values in the developing and validation groups were 0.935 and 0.934, respectively, indicating that this comprehensive nomogram obtained a better discriminatory power than any single independent predictor.

3.3. Prognostic nomogram construction and validation for RCC patients with LM

Univariate and multivariate Cox analyses were used to determine independent risk predictors for RCC patients with LM, including age; histological type; T stage; N stage; surgery; residence; and bone, liver, and brain metastases (Table 3). Age at diagnosis, T stage, N stage, residential area, surgery, metastatic sites, and histological type were identified as independent predictors of OS in patients with lung MRCC ($P < .05$). T stage, N stage, residential area, surgery, metastatic sites, and histological type were selected as independent prognostic markers for CSS in RCC patients with LM ($P < 0.05$). Based on the above outcomes, we constructed 2 nomograms that facilitate effortless prediction of 1-, 3-, and 5-year OS and CSS rates (Fig. 3).

Furthermore, the OS and CSS nomograms were validated using ROC curves and DCA (Fig. 4). ROC analysis revealed AUC values for OS at 1, 3, and 5 years of 0.73, 0.764, and

Table 1

Histopathology and clinical characteristics of renal cell carcinoma patients in the training cohort and validation group.

	Entire cohort (n = 10,929)		
	Training set	Validation set	
Variables	**(n = 5465)**	**(n = 5464)**	***P* value**
Age, yr (%)			.005
<55	1864 (34.1)	1866 (34.1)	
55–73	2841 (52.0)	2948 (54.0)	
>73	760 (13.9)	650 (11.9)	
Fuhrman grade, n (%)			.956
Well differentiated; grade I	603 (11.0)	598 (10.9)	
Moderately differentiated; grade II	2766 (50.6)	2795 (51.2)	
Poorly differentiated; grade III	1690 (30.9)	1670 (30.6)	
Undifferentiated; grade IV	406 (7.5%)	401 (7.3%)	
Laterality, n (%)			.315
Left	2668 (48.8)	2720 (49.8)	
Right	2797 (51.2)	2744 (50.2)	
T stage, n (%)			.955
T1	3604 (65.9)	3626 (66.4)	
T2	582 (10.6)	584 (10.7)	
T3	1224 (22.5)	1199 (21.9)	
T4	55 (1.0)	55 (1.0)	
Pathology			<.001
Clear cell carcinoma	4298 (78.6%)	4343 (79.4%)	
Papillary cell carcinoma	754 (13.8%)	238 (4.4%)	
Chromophobe cell carcinoma	339 (6.2%)	793 (14.5%)	
Collecting duct carcinoma	14 (0.3%)	9 (0.2%)	
Sarcomatoid dedifferentiation	60 (1.1%)	81 (1.5%)	
Median household Income			.883
<$50,000	777 (14.2%)	789 (14.4%)	
$50,000–$75,000	2988 (54.7%)	2997 (54.9%)	
>$75,000	1700 (31.1%)	1679 (30.7%)	
Lymphadenectomy scope			.685
None	4850 (88.7%)	4821 (88.2%)	
1–3 regions	355 (6.5%)	375 (6.9%)	
4 to more regions	260 (4.8%)	268 (4.9%)	
Surgery, n (%)			.725
Yes	5314 (97.2)	5319 (97.3)	
No	151 (2.8)	145 (2.7)	
N stage, n (%)			.976
N0	5232 (95.6)	5225 (95.6)	
N1	114 (2.1)	114 (2.1)	
N2	87 (1.6)	87 (1.6)	
Nx	38 (0.7)	38 (0.7)	
Bone metastasis			.213
Yes	110 (2.0%)	129 (2.4%)	
No	5355 (98.0)	5335 (97.6)	
Liver metastasis			.538
Yes	45 (0.8%)	51 (0.9%)	
No	5420 (99.2%)	5413 (99.1%)	
Brain metastasis			.578
Yes	43 (0.8%)	38 (0.7%)	
No	5422 (99.2%)	5426 (99.3%)	
Lung metastasis			.538
Yes	259 (4.7%)	254 (4.6%)	
No	5206 (95.3%)	5210 (95.4%)	
Tumor size (mm)			.174
<76	4305 (78.8%)	4364 (79.9%)	
76–96	555 (10.2%0	498 (9.1%)	
>96	605 (11.0%)	602 (11.0%)	
Gender, n (%)			.837
Male	3474 (63.6)	3463 (63.4)	
Female	1991 (36.4)	2001 (36.6)	
Race, n (%)			.578
White	4370 (80.0)	4381 (80.2)	
Black	555 (10.1)	558 (10.2)	
Asian	469 (8.6)	441 (8.1)	
American Indian	71 (1.3)	84 (1.5)	

Table 2

Univariate and multivariate logistic regression analysis of associated factors for developing lung metastasis in the developing cohort.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (yr)				
<55	Referent		Referent	
55–73	1.130 (0.852–1.498)	.396	0.818 (0.639–1.047)	.111
>73	1.304 (0.889–1.914)	.174	0.851 (0.596–1.216)	.377
Race, n (%)				
White	Referent		Referent	
Black	0.556 (0.327–0.946)	.030	0.916 (0.464–1.809)	.800
Asian	1.416 (0.959–2.092)	.080	1.833 (1.138–2.952)	.013
American Indian	1.516 (0.604–3.803)	.375	2.121 (0.698–6.443)	.185
Male/female	1.612 (1.217–2.135)	.001	1.147 (0.899–1.464)	.102
Fuhrman grade, n (%)				
Well differentiated	Referent		Referent	
Moderately differentiated	2.533 (0.908–7.062)	.076	2.257 (0.643–7.924)	.204
Poorly differentiated	11.138 (4.093–30.308)	<.001	5.276 (1.513–18.401)	.009
Undifferentiated grade IV	43.876 (15.975–120.505)	<.001	8.223 (2.281–29.646)	.001
Right/left	0885 (0.689–1.136)	.336		
T stage, n (%)				
T1	Referent		Referent	
T2	13.270 (7.799–22.581)	<.001	3.033 (1.505–6.110)	.002
T3	26.770 (16.915–42.368)	<.001	6.258 (3.467–11.294)	<.001
T4	204.743 (103.475–405.119)	<.001	10.826 (4.322–27.118)	<.001
Tumor size (mm)				
<76	Referent		Referent	
76–96	9.564 (6.728–13.596)	<.001	2.005 (1.254–3.207)	.004
>96	17.257 (12.585–23.663)	<.001	3.134 (2.036–4.823	<.001
Pathology				
Clear cell carcinoma	Referent		Referent	
Papillary cell carcinoma	0.218 (0.111–0.426)	<.001	0.383 (0.183–0.802)	.011
Chromophobe cell carcinoma	0.161 (0.051–0.505)	.002	0.181 (0.051–0.645)	.008
Collecting duct carcinoma	1.386 (0.181–10.642)	.754	0.205 (0.020–2.088)	.181
Sarcomatoid dedifferentiation	9.009 (5.181–15.665)	<.001	1.277 (0.570–2.862)	.552
Surgery (yes/no)	0.063 (0.044–0.090)	<.001	0.077 (0.042–0.141)	<.001
N stage, n (%)				
N1/N0	13.931 (9.189–21.122)	<.001	2.318 (1.309–4.106)	.004
N2/N0	13.858 (8.540–22.487)	<.001	2.229 (1.180–4.211)	.013
Nx/N0	20.164 (10.224–39.767)	<.001	2.736 (0.989–7.570)	.053
Lymphadenectomy scope				
None	Referent			
1–3 regions	3.869 (3.022–4.954)	<.001	0.851 (0.526–1.375)	.509
4 to more regions	5.650 (4.389–7.273)	<.001	1.207 (0.710–2.049)	.487
With bone metastasis (yes/no)	18.098 (12.108–27.053)	<.001	0.363 (0.212–0.622)	<.001
With liver metastasis (yes/no)	63.201 (32.212–124.005)	<.001	0.212 (0.093–0.483)	<.001
With brain metastasis (Yes/no)	37.751 (20.062–71.036)	<.001	0.177 (0.081–0.389)	<.001
Median household Income				
<$50,000	Referent			
$50,000–$75,000	1.074 (0.732–1.576)	.714		
>$75,000	1.150 (0.766–1.728)	.501		
Urban/rural	0.731 (0.520–1.027)	.071	0.926 (0.607–1.414)	.723

CI = confidence interval, HR = hazard ratio.

0.777, respectively. The AUC values for CSS at 1, 3, and 5 years were 0.73, 0.761, and 0.761, respectively. In general, an AUC value >0.7 for the prediction of OS and CSS indicates excellent discriminatory power of the nomogram. The DCA curve also revealed that these nomograms demonstrated significantly better predictive ability than the AJCC staging system.

4. Discussion

The lung is one of the most common sites of metastases for a variety of solid tumors, including gastric, renal, breast, and thyroid cancers; LM occurs in 43.6% of metastatic renal cancers.[10] Unfortunately, LM generally involves palliative rather than curative treatment and has adverse outcomes. Currently, there are very few published studies on the predictive indicators and prognostic factors of lung MRCC. The purpose of our study was to construct a predictive and prognostic model for RCC patients with LM and evaluate the accuracy of these models. The nomogram is an intuitive graph based on multivariate regression analyses outcomes, which can quantify all independent risk factors and facilitate the development of personalized therapeutic management.[11]

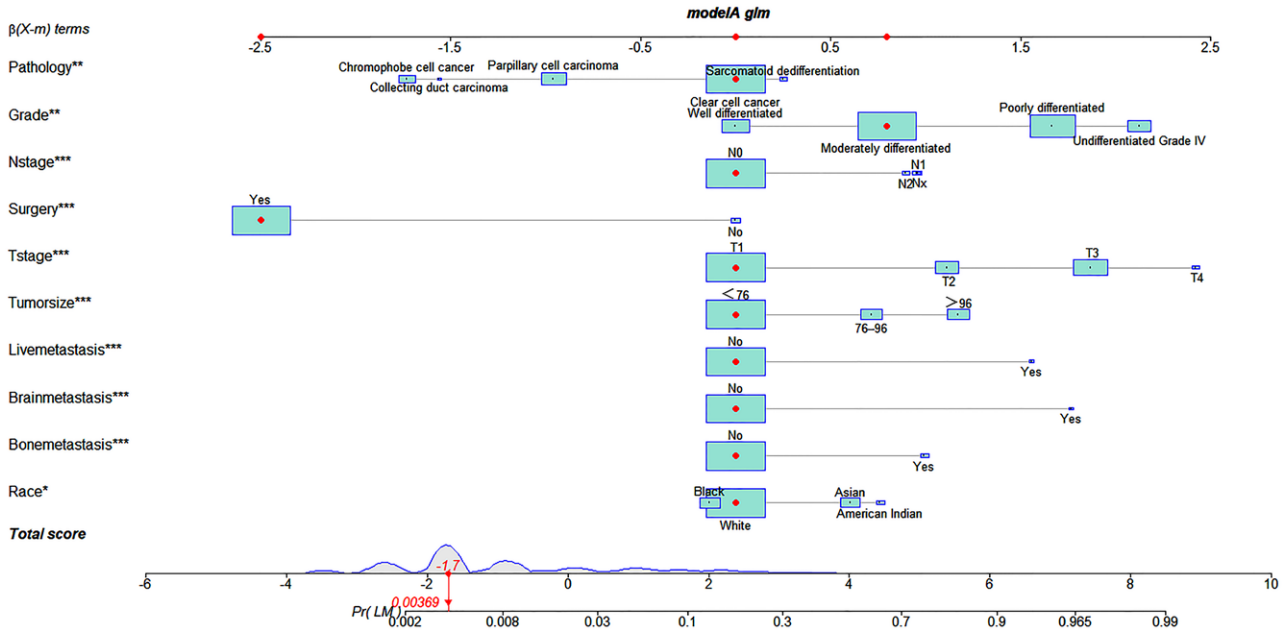

Figure 1. Nomogram to predict risk of lung metastasis in renal cell cancer patients. The values of each independent predictor for individual patients are associated with the variable axes, and a line is drawn upward to the value axis to determine the points of each variable. The total points axis at the bottom of the nomogram and each independent risk factor score are summed to obtain the total points. Then, a vertical line is drawn from the total points axis to the lung metastasis scale to obtain the probability.

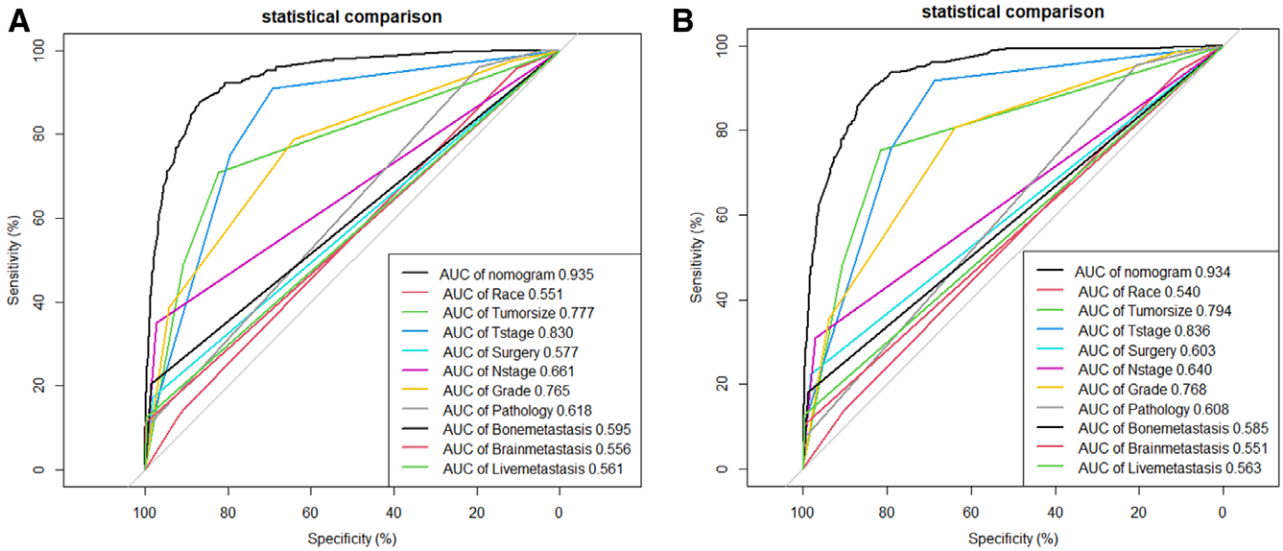

Figure 2. Comparison of receiver operating characteristic curves and areas under the curve between predictive nomogram and each independent predictor in the developing group (A) and validation cohort (B). AUC = area under curve.

Conventional research has demonstrated some factors that potentially predict LM in RCC patients, such as tumor size, tumor grade, race, and histologic subtype.[10] These factors were also included in the current study. After multivariate logistic analysis based on SEER data from 2010 to 2015, histological type; T stage; tumor grade; N stage; surgery; race; tumor size; bone, liver, and brain metastases were identified as independent predictive factors for LM.

Hou et al[5] reported that sarcomatoid RCC has a high incidence of LM (33.6%), which is related to poor prognosis. Here, we also found that sarcomatoid RCC patients were most likely to develop LM compared with other pathological types of RCC. However, compared with sarcomatoid RCC with LM, collecting duct carcinoma with LM had a significantly worse prognosis, according to our newly developed nomogram.

Many previous studies have subjectively classified patients into different age groups and tumor size cohorts, which might have led to statistical deviations. To resolve this issue, we used X-tile to determine the best cutoff values for tumor size and age at initial diagnosis in lung MRCC patients based on survival status. Hua and Hu[12] demonstrated that older age (>70 years) may be associated with worse OS and CSS compared with younger patients with MRCC. Similar to our results, older lung MRCC patients (age at diagnosis>73 years) were significantly associated with a worse prognosis compared with younger patients. However, age was neither an independent risk factor

Table 3

Univariate and multivariate Cox analyses associated with OS and CSS of lung metastatic RCC.

	OS of RCC patients with LM (n = 513)				CSS of RCC patients with LM (n = 513)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (yr)								
<55	Referent				Referent		Referent	
55–73	1.165 (0.917–1.479)	.211	1.208 (0.942–1.551)	.137	1.137 (0.889–1.454)	.307	1.225 (0.946–1.588)	.124
>73	1.661 (1.202–2.293)	.002	1.610 (1.146–2.264)	.006	1.358 (0.957–1.927)	.087	1.321 (0.912–1.913)	.141
Race, n (%)								
White	Referent		Referent		Referent			
Black	1.236 (0.777–1.966)	.372	0.994 (0.609–1.623)	.981	1.211 (0.742–1.978)	.444		
Asian	0.712 (0.501–1.011)	.057	0.793 (0.550–1.144)	.215	0.738 (0.514–1.060)	.100		
American Indian	0.642 (0.303–1.359)	.247	0.516 (0.240–1.107)	.089	0.711 (0.335–1.506)	.373		
Gender, n (%)								
Male/female	0.963 (0.764–1.212)	.746			1.004 (0.787–1.280)	.976		
Fuhrman grade, n (%)								
Well differentiated	Referent				Referent		Referent	
Moderately differentiated	0.557 (0.268–1.158)	.117			0.510 (0.244–1.065)	.073	0.577 (0.269–1.238)	.158
Poorly differentiated	0.652 (0.320–1.329)	.239			0.592 (0.290–1.207)	.149	0.774 (0.364–1.646)	.506
Undifferentiated; grade IV	0.643 (0.315–1.315)	.226			0.616 (0.301–1.261)	.185	0.812 (0.372–1.771)	.601
Laterality, n (%)								
Right/left	0.882 (0.716–1.087)	.240			0.855 (0.687–1.064)	.160		
T stage, n (%)								
T2/T1	1.124 (0.726–1.742)	.600	0.848 (0.531–1.355)	.491	1.168 (0.740–1.844)	.505	0.894 (0.547–1.459)	.653
T3/T1	1.105 (0.760–1.607)	.601	1.196 (0.814–1.758)	.361	1.095 (0.739–1.623)	.652	1.177 (0.780–1.775)	.438
T4/T1	2.158 (1.293–3.601)	.003	2.360 (1.383–4.026)	.002	2.265 (1.334–3.848)	.002	2.388 (1.368–4.171)	.002
Tumor size (mm)								
<76	Referent				Referent			
76–96	1.129 (0.847–1.504)	.409			1.159 (0.858–1.566)	.336		
>96	1.137 (0.886–1.459)	.312			1.176 (0.906–1.528)	.224		
Pathology								
Clear cell carcinoma	Referent		Referent		Referent			
Papillary cell carcinoma	2.508 (1.510–4.167)	<.001	2.578 (1.497–4.439)	.001	2.520 (1.492–4.257)	.001	2.540 (1.449–4.454)	.001
Chromophobe cell carcinoma	0.566 (1.140–2.288)	.425	0.487 (0.117–2.023)	.322	0.665 (0.164–2.688)	.567	0.599 (0.144–2.488)	.481
Collecting duct carcinoma	4.268 (1.581–11.524)	.004	2.508 (0.883–7.122)	.084	4.500 (1.665–12.159)	.003	2.407 (0.840–6.903)	.102
Sarcomatoid dedifferentiation	1.990 (1.400–2.829)	<.001	1.761 (1.229–2.522)	.002	2.111 (1.475–3.020)	<.001	1.682 (1.136–2.490)	.009
Surgery, n (%)								
Yes/no	0.403 (0.307–0.528)	<.001	0.541 (0.382–0.766)	.001	0.384 (0.291–0.506)	<.001	0.447 (0.307–0.650)	<.001
N stage, n (%)								
N1/N0	1.662 (1.259–2.194)	<.001	1.343 (0.996–1.810)	.053	1.582 (1.180–2.121)	.002	1.229 (0.895–1.687)	.203
N2/N0	1.975 (1.429–2.729)	<.001	1.794 (1.275–2.523)	.001	1.920 (1.368–2.694)	<.001	1.633 (1.135–2.350)	.008
NX/N0	1.559 (0.939–2.589)	.086	1.456 (0.868–2.442)	.154	1.567 (0.928–2.646)	.093	1.370 (0.805–2.330)	.246
Lymphadenectomy scope								
None	Referent							
1–3 regions	0.999 (0.757–1.318)	.995			0.984 (0.736–1.316)	.912		
4 to more regions	0.975 (0.741–1.282)	.855			0.941 (0.705–1.256)	.681		
With bone metastases								
Yes/no	1.990 (1.539–2.573)	<.001	1.963 (1.492–2.582)	<.001	2.041 (1.566–2.661)	<.001	1.969 (1.487–2.608)	<.001
With liver metastases								
Yes/no	1.750 (1.270–2.411)	.001	1.467 (1.036–2.078)	.031	1.796 (1.293–2.495)	<.001	1.515 (1.063–2.160)	.022
With brain metastases								
Yes/no	2.315 (1.634–3.282)	<.001	2.080 (1.405–3.081)	<.001	2.427 (1.702–3.462)	<.001	2.108 (1.416–3.140)	<.001
Median household income								
<$50,000	Referent				Referent			
$50,000–$75,000	0.874 (0.632–1.207)	.413			0.799 (0.572–1.115)	.187		
>$75,000	0.867 (0.612–1.227)	.420			0.861 (0.604–1.228)	.409		
Residence								
Urban/rural	0.763 (0.582–1.001)	.051	1.358 (1.027–1.797)	.032	1.335 (1.008–1.767)	.044	1.424 (1.067–1.899)	.016

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, LM = lung metastasis, OS = overall survival, RCC = renal cell carcinoma.

for LM nor a significant prognostic factor for CSS. Tong et al[13] reported that a tumor size ≥7 cm may have a higher risk of metastasis in RCC patients. In accordance with this study, we demonstrated that RCC patients with tumor sizes ≥96 mm may have a 3.1-fold higher risk for LM than patients with tumor sizes <76 mm. Therefore, we considered that there was a positive correlation between tumor size and LM in RCC patients, whereas tumor size did not significantly influence OS or CSS, possibly because the majority of the included patients underwent surgery.

Regarding RCC, several researchers have reported that T and N stages are independent predictive factors for tumor metastasis and prognosis of metastatic tumors.[12,14] In the present study, we found that T and N stages not only predicted the incidence of LM but were also significantly related to the OS and CSS of lung MRCC patients. In the past decade, the role of surgery in the therapeutic strategy for metastatic RCC in the era of molecular targeted therapy has been debated. Multiple retrospective studies have shown that metastatic RCC patients receiving targeted drug therapy can obtain survival benefits following surgery.[15,16] Nevertheless, Mason et al[17] reported that whether metastatic RCC patients benefit from nephrectomy mainly depends on the patient's health status. Specifically, metastatic RCC patients in good condition who received primary tumor surgery were more likely to gain a survival advantage. In our analysis, nephrectomy was an important factor for predicting the possibility of LM and played a critical role in survival benefits, even in RCC patients with LM who underwent

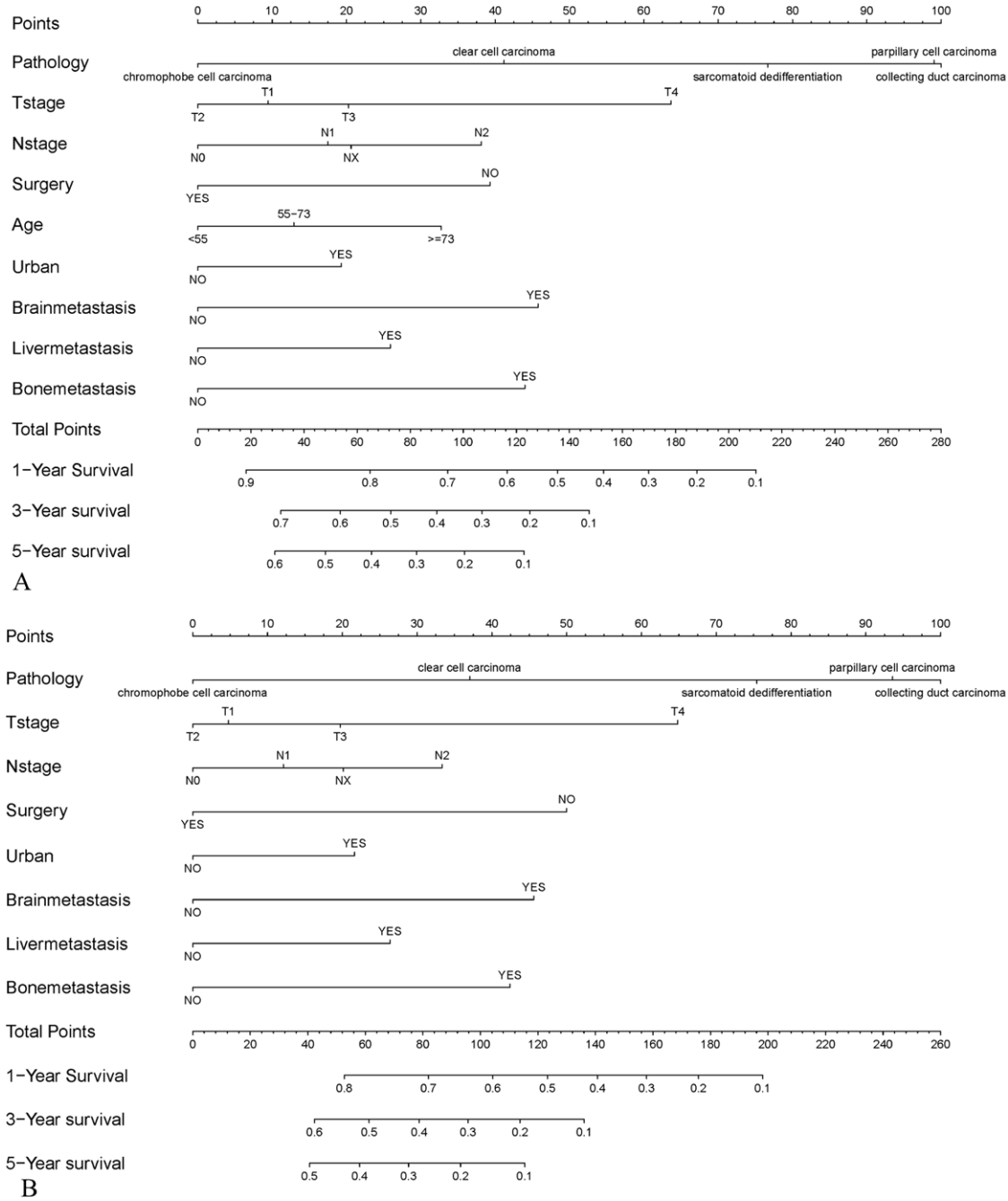

Figure 3. Nomograms that predict the 1-, 3-, and 5-yr OS and CSS rates of lung metastatic renal cell cancer. The values of each independent predictor for individual patients are located at the variable axes. Draw a line upward from each site to the axis point to obtain the points of each variable. Sum the points of each variable located on the total points axis at the bottom of the nomogram. From the total points axis, draw a vertical line downward to predict the 1-, 3-, and 5-year OS and CSS probability. (A) Prediction of 1-, 3-, and 5-yr OS probability and (B) prediction of 1-, 3-, and 5-yr CSS probability. CSS = cancer-specific survival, OS = overall survival.

incomplete resection. Therefore, we recommend surgery with caution for lung MRCC patients.

Until now, routine lymphadenectomy and the scope of lymph node dissection in nephrectomy have been controversial. Whitson et al[18] reported that lymphadenectomy could improve the 5-year survival rate of RCC patients with only lymph node metastasis.[19] Previous studies have shown that regional lymphadenectomy and enlarged regional dissection are statistically indistinguishable.[20,21] In this study, we found that routine lymphadenectomy or enlarged lymph node dissection did not significantly reduce the possibility of LM or the 1-, 3-, and 5-year survival rates of lung MRCC.

At present, RCC patients are the most prone to metastasis to the lung tissue, followed by the bone, liver, and brain. There are few reports on whether metastasis to one organ prompts metastasis to other organs. Some scholars have shown that LM and bone metastasis can improve the incidence of brain metastasis in RCC patients.[16] Fan et al[22] demonstrated that LM, brain metastasis, and liver metastasis could increase the possibility of bone metastasis in RCC patients. Similar to a previous study, we found that bone, brain, and live metastases could increase the rates of LM. Therefore, we suspected that metastatic tumor organs could mutually promote metastasis, which requires multicenter clinical studies and large data sets for validation.

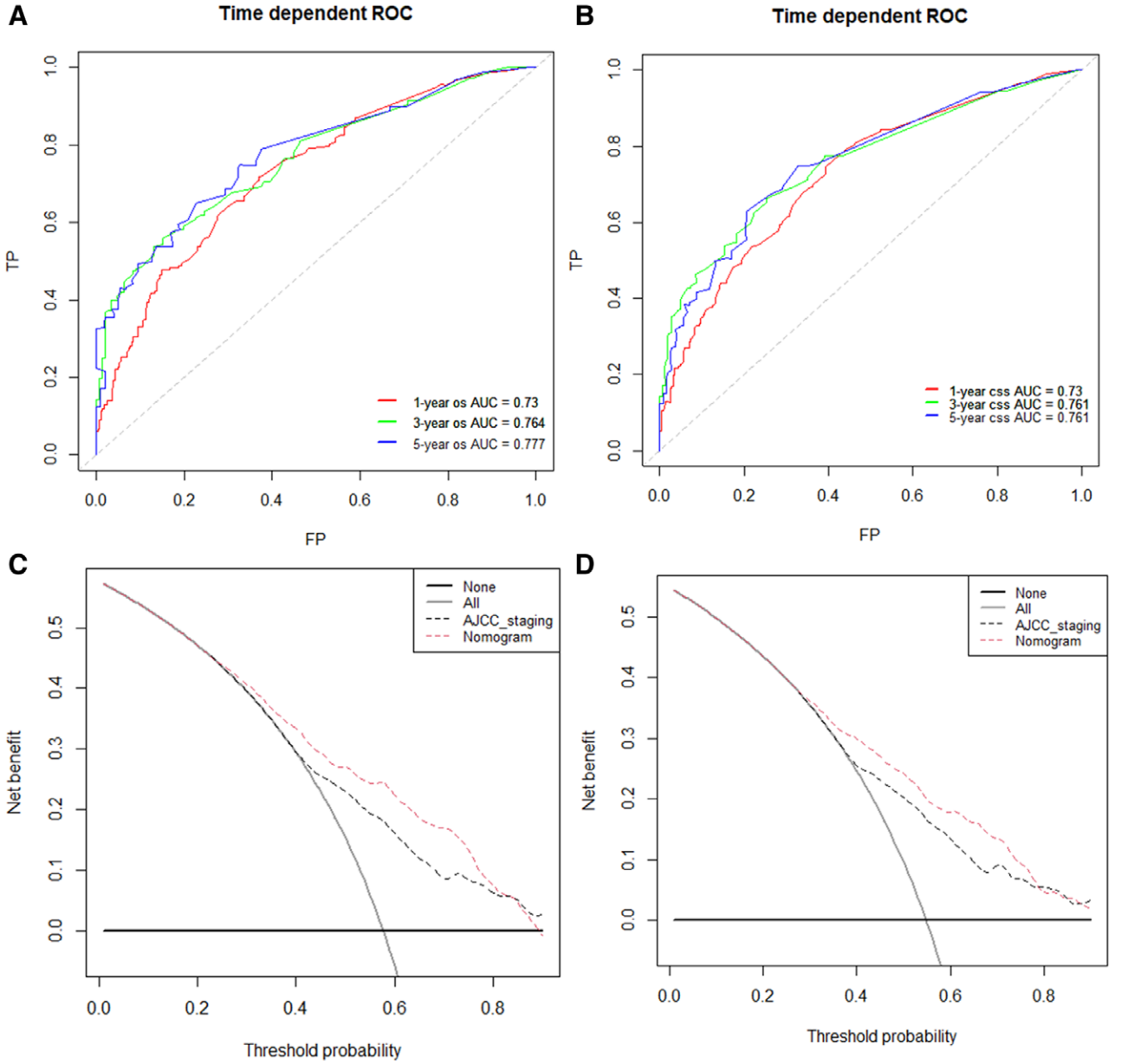

Figure 4. ROC curve to validate the predictive accuracy of the nomograms. (A) 1-, 3-, and 5-yr OS accuracy and (B) 1-, 3-, and 5-yr CSS accuracy. Comparison of predictive values of nomograms and AJCC staging system for the prediction of lung metastatic renal cell cancer. (C) Decision curve analysis of OS and (D) decision curve analysis of CSS. AJCC = American Joint Committee on Cancer, AUC = area under curve, CSS = cancer-specific survival, OS = overall survival, ROC = receiver operating characteristic, TP = true positives

Currently, there is no consensus regarding the relationship between race and tumor metastasis. Pecoraro et al[10] reported that Black RCC patients were more likely to have tumor metastasis than White RCC patients. In our research, Asian and American-India populations had higher scores when predicting LM than White populations. However, no statistical differences were found among the various races and survival times. There are few existing reports on the association between residence and prognosis of MRCC patients. Indeed, air pollution poses a great challenge for urban areas. Many researchers have reported that air pollution is strongly associated with LM and lung cancer.[23–25] Based on our nomogram, we believe living in urban areas has serious adverse impacts on the OS and CSS of lung MRCC patients, and that residence may be an important prognostic indicator for lung MRCC patients.

Although these 3 effective nomograms have illustrated satisfactory predictive power for lung MRCC patients, the current study is not without limitations. Bias might have been reduced if the SEER database had included more information, such as comorbidities, personal information, laboratory test results, specific treatment information, and complications. Additional multicenter studies with large sample sizes are required in the future to further validate out predictive and prognostic models.

5. Conclusions

We created 3 excellent predictive nomograms for RCC patients with LM. One model can accurately predict the incidence of LM in RCC patients and the other 2 can precisely analyze the OS

and CSS of lung MRCC patients. In the future, these models may contribute to individualized treatment for lung MRCC patients.

Acknowledgments

The authors acknowledge the support by the Science Research Fund Project of Anhui Medical University in Anhui Province (2019XKJ166), the Natural Science Fund of University of Anhui Province (KJ2018A0457), the College Excellent Youth Talent Support Program of Anhui Province (gxyq2019081), and the Open Fund for Discipline Construction, Institute of Physical Science and Information Technology, Anhui University (OEIAM202008).

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