

# An immune scores-based nomogram for predicting overall survival in patients with clear cell renal cell carcinoma

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## Abstract

The role of immune cell infiltration in the prognosis of clear cell renal cell carcinoma (ccRCC) has received increasing attention. However, immune scores have not yet been introduced into routine clinical practice of ccRCC patients. The principal objective of our research was to study the correlation between immune scores and overall survival (OS) of ccRCC.

In this study, Cox regression analyses were used to identify risk factors associated with OS of ccRCC based on the Cancer Genome Atlas datasets. Furthermore, an integrated nomogram combining immune scores and clinicopathologic factors was built for predicting 3- and 5-year OS of ccRCC patients. The receiver operating characteristic curve, concordance index, and calibration curves were used for the evaluation of our nomogram. Also, Kaplan–Meier (KM) survival analysis of immune scores, stromal scores, and different clinicopathological factors was performed.

A total of 514 patients were divided into the low- or high-immune scores group. KM and multivariate Cox regression analyses demonstrated that ccRCC patients with high-immune scores had significantly poor OS compared with those with low-immune scores. Calibration curves showed good consistency between the predicted OS and the actual OS probability. Areas under the receiver operating characteristic curves for 3- and 5-year OS were 0.816 and 0.769, and the concordance index was 0.775, indicating that our nomogram had good accuracy for predicting OS of ccRCC patients. Additionally, KM analysis showed that older age, later T stage, distant metastasis, advanced tumor lymph node metastasis stage, higher tumor grade, left site, and low stromal scores were associated with worse OS in ccRCC patients.

High-immune scores show a significant correlation with unsatisfactory prognosis in ccRCC patients. Furthermore, the immune scores-based nomogram may be helpful in predicting ccRCC prognosis.

**Abbreviations:** AUC = area under the curve, ccRCC = clear cell renal cell carcinoma, CI = confidence intervals, c-index = concordance index, ESTIMATE = estimation of stromal and immune cells in malignant tumor tissues using expression data, HR = hazard ratio, IQR = interquartile range, KM = Kaplan–Meier, OS = overall survival, RCC = renal cell carcinoma, ROC = receiver operating characteristic, TCGA = the Cancer Genome Atlas, TNM stage = tumor lymph node metastasis stage.

**Keywords:** clear cell renal cell carcinoma, immune scores, nomogram, prognosis

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

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## 1. Introduction

Renal cell carcinoma (RCC) is the most common malignant tumor in kidney, and more than 350,000 cases diagnosed with RCC each year are estimated.<sup>[1]</sup> The most common type of RCC is clear cell renal cell carcinoma (ccRCC), which accounts for the majority of kidney cancer deaths.<sup>[2]</sup> In spite of significant advances in diagnostic and therapeutic strategies, the incidence, and mortality of ccRCC are still increased year by year.<sup>[3]</sup> In recent years, immunotherapy has achieved success in treating ccRCC, but not all ccRCC patients benefited from such treatment.<sup>[4,5]</sup> Thus, it is critical to identify new and reliable prognostic tools able to predict the prognosis and guide clinical therapy.

In previous years, the relationship between cancer micro-environments and the prognosis of ccRCC has gained more and more attention.<sup>[6]</sup> It has been reported that immune cells and stromal cells in the tumor microenvironment play a crucial role in regulating the biological processes of cancer cells.<sup>[7]</sup> Previous research has shown that immune scores calculated by gene expression data can be used to infer the infiltration of immune cells and stromal cells in cancer tissues.<sup>[8]</sup> In addition, several studies also reported that immune infiltration is correlated with the prognosis of patients with ccRCC.<sup>[7,9,10]</sup> Nevertheless, these

findings have not yet been incorporated into the regular clinical practice of patients with ccRCC. Recently, nomograms have been extensively used to predict the prognosis of patients with cancers, such as hepatocellular carcinoma,<sup>[11]</sup> colorectal cancer,<sup>[12]</sup> and ccRCC.<sup>[13]</sup> However, nomogram combining immune scores and clinical factors for the prognosis of ccRCC has not been reported. In the present study, we aimed to assess the correlation between immune scores and the prognosis of patients with ccRCC and to establish an integrated nomogram combining immune scores and clinicopathologic factors to predict the prognosis of ccRCC.

## 2. Methods

### 2.1. Data collection and processing

In the present study, the Cancer Genome Atlas (TCGA) clinical data of ccRCC was acquired from cBio Cancer Genomics Portal database (<http://www.cbioportal.org/>).<sup>[14,15]</sup> The cBio Cancer Genomics Portal was designed to make the raw data generated by large-scale cancer genomic projects more directly and easily available, and it includes many provisional TCGA datasets.<sup>[14]</sup> Data, including age, sex, stage (T/M/tumor lymph node metastasis stage (TNM)), grade, laterality, history of other malignancy, survival time, and vital status were extracted from the TCGA datasets. Then, immune and stromal scores of TCGA ccRCC dataset were downloaded from ESTIMATE (estimation of stromal and immune cells in malignant tumor tissues using expression data, <https://bioinformatics.mdanderson.org/estimate/disease.html>). Immune and stromal scores of each patient can reflect the gene signature enrichment of stromal and immune cells.<sup>[16]</sup> The previous study has proposed a method to obtain immune scores or stromal scores to infer the degree of infiltration of immune or stromal cells. For instance, the immune signature was acquired by comparing the gene expression profiles of normal hematopoietic cells with that of other normal samples, which stood for the infiltration of immune cells in cancer tissues.<sup>[8]</sup> Subsequently, immune or stromal scores were matched to clinical and survival data of TCGA by sample ID codes. Besides, TCGA samples with incomplete clinicopathological information or survival data were removed. The clinical data of ccRCC is publicly available in TCGA database, so the ethical approval is not required for this study.

### 2.2. Correlation between immune scores and clinicopathological features

Determination of the optimal cut-off values for stromal and immune scores was performed using the X-tile (Version 3.6.1; Yale University School of Medicine, New Haven, CT, USA).<sup>[17]</sup> After that, TCGA samples of ccRCC were classified into low- and high-immune/stromal scores groups. Comparisons of categorical data between the immune score subgroups and different clinicopathological characteristics were performed by  $\chi^2$  (Chi-squared) test or Fisher exact test (as appropriate) using IBM SPSS Statistics 22 (Chicago, IL).

### 2.3. Establishment of the prognostic nomogram based on immune scores

Before establishing the nomogram, stromal scores, immune scores, and the clinicopathological factors (including sex, age, T stage, distant metastasis status, TNM stage, tumor grade,

laterality, and history of other malignancy) were subjected to univariate Cox regression analysis. Then, variables with statistical significance in univariate analysis were included in the multivariate Cox regression analysis. According to the results of Cox regression analyses, an immune scores-based nomogram was constructed for predicting 3- and 5-year survival rates of ccRCC patients. Calibration plots were used to assess the prognostic accuracy of the nomogram, and internal validation was performed using 1000 bootstrap resamples. A bootstrap method is the preferred approach for internal verification, especially when a large number of candidate predictors are studied.<sup>[18]</sup> Moreover, the time-dependent receiver operating characteristic (ROC) curves and concordance index (c-index) were utilized to measure the predictive ability of the nomogram. In the present study, Cox regression analyses, nomogram establishment, and calibration curves were performed using “survival” and “rms” packages of R version 3.6.0 (<http://www.r-project.org>; The R Foundation for Statistical Computing, Vienna, Austria). And ROC curves were generated using “survival ROC” package of R software. In addition, results of multivariable Cox analysis were presented using a forest plot with R package “survminer”.

### 2.4. Statistical analysis

The primary outcome of our study was overall survival (OS) which was defined as the time between the date of diagnosis and the date of death from any cause. Additionally, enumeration data were expressed in percentage (%), measurement data with non-normal distribution were shown as median (interquartile range (IQR)), measurement data with normal distribution were presented as mean (standard deviation). Hazard ratio (HR) with 95% confidence intervals (CI) were calculated and reported based on the Cox regression model. Furthermore, the difference in survival among immune scores groups was analyzed by Kaplan–Meier (KM) method using R “survival” and “survminer” packages. All the statistical tests were 2-sided, and *P*-values less than .05 were considered statistically significant.

## 3. Results

### 3.1. Characteristics of ccRCC patients

After data matching and cleaning, a total of 514 ccRCC patients with complete prognosis information were included for further analyses, and the detailed screening process is presented in Figure 1. In the TCGA ccRCC dataset, each immune score corresponded to a ccRCC patient. The median age (IQR) of the ccRCC patients was 60 (52–70), ranging from 26 to 90 years, of which 257 (50%) patients were above 60 years old. Among 514 patients with ccRCC, 327 (63%) were in T1 and T2 stage, 205 (40%) were at pathological TNM stages III-IV, and distant metastasis was detected in 82 patients (16%). The average immune score of ccRCC patients was 1110.44 (standard deviation=727.16), and the median OS time (IQR) of the patients was 40.21 (18.49–63.42) months, ranging from 0 to 149.05 months. Also, the best cut-off value for immune scores was 1180 according to the X-tile, and then ccRCC patients were classified into low- and high-immune scores groups. The optimal cut-off value of stromal scores was 65.4, and ccRCC patients were also categorized into low- and high-stromal scores subgroups.

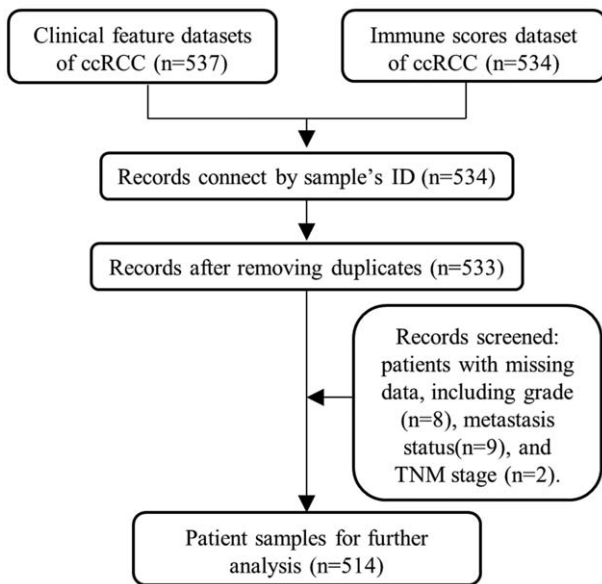


Figure 1. The detailed flow diagram of sample selection.

**Table 1**  
Correlations between clinicopathological features and immune scores.

Features	Total	Immune scores		$\chi^2$ value	P-value
		Low	High		
Sample sizes	514	281	233	-	-
Age				3.656	.455
<=50	110	57 (20.28%)	53 (22.75%)		
51-60	147	81 (28.83%)	66 (28.33%)		
61-70	136	70 (24.91%)	66 (28.33%)		
71-80	99	62 (22.06%)	37 (15.88%)		
81-90	22	11 (3.91%)	11 (4.72%)		
Sex				3.255	.710
Female	178	107 (38.08%)	71 (30.47%)		
Male	336	174 (61.92%)	162 (69.53%)		
T stage				9.002	.029
T1	262	160 (56.94%)	102 (43.78%)		
T2	65	30 (10.68%)	35 (15.02%)		
T3	176	86 (30.60%)	90 (38.63%)		
T4	11	5 (1.78%)	6 (2.58%)		
Metastasis				8.192	.004
M0	432	248 (88.26%)	184 (78.97%)		
M1	82	33 (11.74%)	49 (21.03%)		
TNM stage				14.607	.002
I	256	159 (56.58%)	97 (41.63%)		
II	53	25 (8.90%)	28 (12.02%)		
III	122	64 (22.78%)	58 (24.89%)		
IV	83	33 (11.74%)	50 (21.46%)		
Grade				21.591	.000
G1	13	10 (3.56%)	3 (1.29%)		
G2	222	141 (50.18%)	81 (34.76%)		
G3	204	103 (36.65%)	101 (43.35%)		
G4	75	27 (9.61%)	48 (20.60%)		
Laterality				2.778	.960
Left	244	124 (86.12%)	120 (51.50%)		
Right	270	157 (13.88%)	113 (48.50%)		
History of other malignancy				0.252	.615
No	439	242 (56.12%)	197 (84.55%)		
Yes	75	39 (13.88%)	36 (15.45%)		
Stromal scores				30.515	.000
Low	72	61 (21.71%)	11 (4.72%)		
High	442	220 (78.29%)	222 (95.28%)		

TNM stage = tumor lymph node metastasis stage.

**Table 2**  
Univariate analysis of clinicopathological factors, stromal and immune scores.

Characteristics	HR (95%CI)	P
Age (<=50)	Reference	
51-60	1.79 (1.06-3.03)	.030
61-70	2.07 (1.23-3.50)	.006
71-80	2.88 (1.70-4.87)	<.001
81-90	3.79 (1.88-7.62)	<.001
Sex (Female)	Reference	
Male	0.96 (0.70-1.31)	.776
T stage (T1)	Reference	
T2	1.56 (0.93-2.60)	.090
T3	3.18 (2.25-4.50)	<.001
T4	10.4 (5.24-20.6)	<.001
Metastasis (M0)	Reference	
M1	4.28 (3.14-5.83)	<.001
TNM stage (I)	Reference	
II	1.26 (0.68-2.33)	.472
III	2.53 (1.68-3.82)	<.001
IV	6.47 (4.42-9.47)	<.001
Grade (G1)	Reference	
G2	7.49e+06 (Inf)	.993
G3	1.35e+06 (Inf)	.993
G4	3.61e+06 (Inf)	.993
Laterality (Left)	Reference	
Right	0.72 (0.53-0.98)	.034
History* (No)	Reference	
Yes	0.86 (0.56-1.32)	.486
Stromal scores (low)		
High	0.60 (0.41-0.88)	.009
Immune scores (Low)		
High	1.54 (1.14-2.09)	.005

\* History of other malignancy.

TNM stage = tumor lymph node metastasis stage.

The clinicopathological features of the low- (<=1180) and high-immune scores (>1180) groups are displayed in Table 1. Medians (IQR) of the low- and high-immune scores groups were 682.92 (409.07-903.97), and 1623.83 (1389.51-2014.69), respectively. As for distant metastasis status, the proportion of M1 in high-immune scores subgroup was higher than that in low-immune scores subgroup. In respect of T stage or TNM stage, ccRCC patients in low-immune scores subgroup tended to be in the early stage. The proportion of G3-G4 was higher than G1-G2 in the high-immune scores group. In addition, patients in low-immune scores group tended to have low stromal scores compared with those in the high-immune scores group.

### 3.2. Results of univariate and multivariate Cox regression analyses for OS

The results of univariate and multivariate Cox regression analyses are summarized in Table 2 and Figure 2, respectively. In the univariate analysis, 71 to 80 age group, 81 to 90 years age group, advanced T stage (T3-T4), late TNM stage (stage III-IV), and high-immune scores were related to worse OS, respectively (P-value<.05). Besides, high-stromal scores group and right laterality were found to be statistically correlated with better OS.

In the multivariate Cox regression analysis, high-immune scores were significantly associated with worse OS (HR: 1.41, 95%CI: 1.02-2.0) compared with low-immune scores. Furthermore, ccRCC patients in the high-stromal scores group had

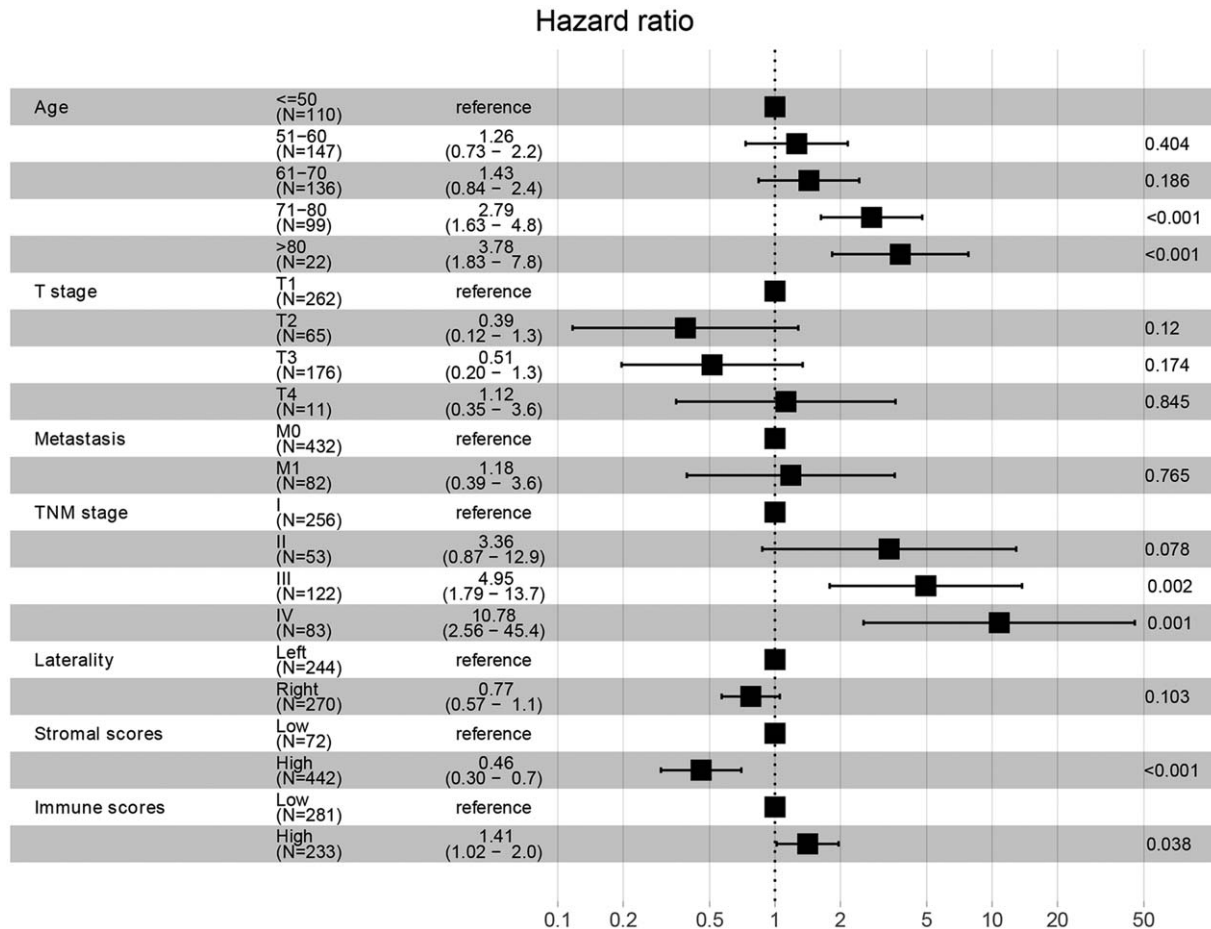


Figure 2. Forest plot with hazard ratios based on multivariate Cox regression analysis.

significantly better OS (HR: 0.46, 95%CI: 0.30–0.70). In addition, patients in the 71 to 80 age group and 81 to 90 age group had a worse OS. Compared with stage I patients, patients with TNM stage III-IV had significantly worse OS. Other factors, including T stage, distant metastasis status, and laterality, were determined to be not statistically significant by multivariate Cox regression analysis.

### 3.3. Immune scores-based nomogram for OS

After taking factors related to immune scores and the Cox regression analysis results together into consideration, the prognostic nomogram for predicting the OS of ccRCC was constructed (Fig. 3). The discrimination capability of the nomogram was verified by the ROC curves, and the area under the curve of 3- and 5-year were 0.816 and 0.769, respectively (Figs. 4A and B). Furthermore, the c-index of the nomogram was 0.775 (95% CI, 0.742–0.808). The calibration plots showed good agreement between nomogram predictions and actual observations, and the results are shown in Figures 4C and 4D.

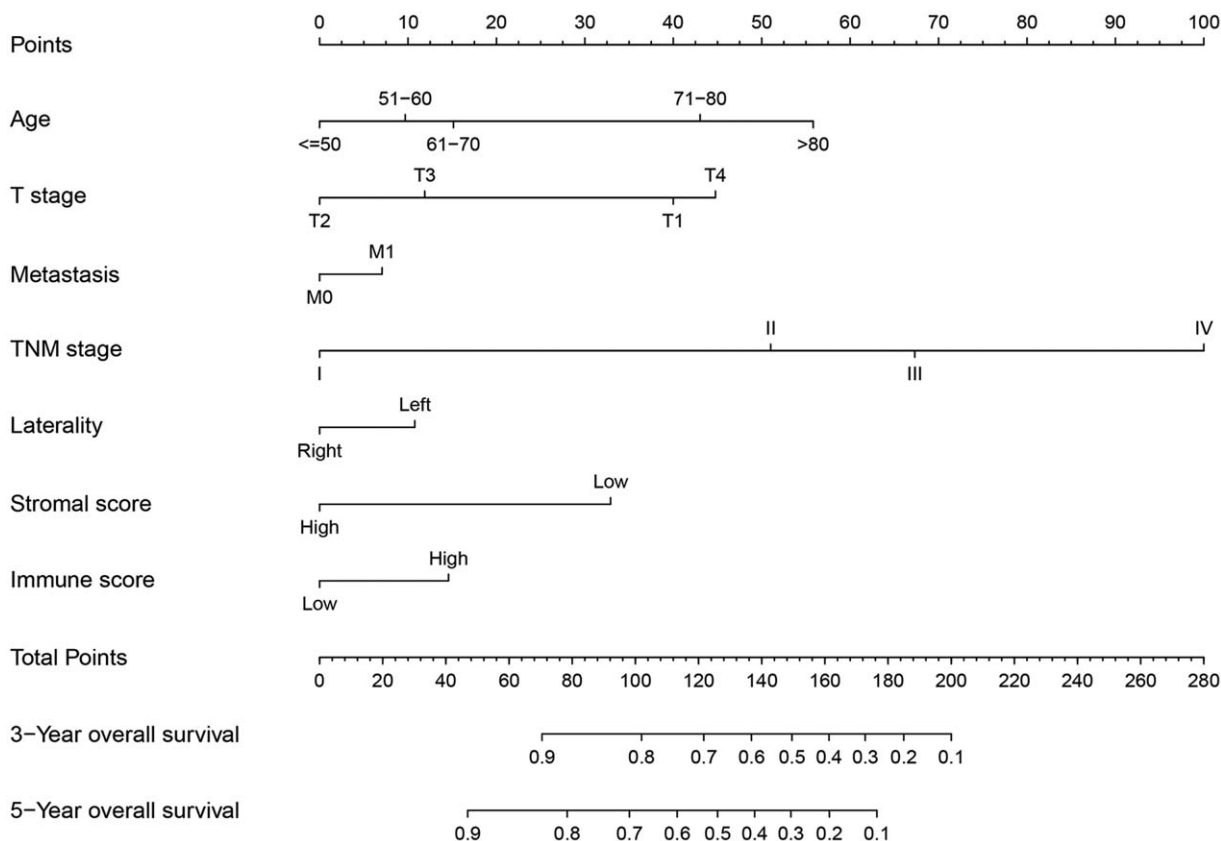
### 3.4. Results of KM survival analysis of OS

The results of survival analysis for the clinicopathological factors, stromal scores, and immune scores are demonstrated in Figures 5A to J. KM survival curves indicated that ccRCC patients with older age, later T stage, distant metastasis,

advanced TNM stage, higher tumor grade, and left-sided tumor had a significantly shorter OS time, and low stromal scores were also related to worse OS. Additionally, OS rate was significantly worse in the high-immune scores group compared with the low-immune scores group. Besides, there was no significant difference with regard to other factor.

## 4. Discussion

In this study, we investigated the prognostic value of immune scores in patients with ccRCC and established an immune scores-based nomogram. Using Cox regression analyses and KM survival curves, we found that the OS time of patients with high-immune scores was significantly worse than that of patients with low-immune scores. Moreover, a nomogram composed of immune scores and clinicopathological characters was built to predict 3- and 5-year OS for ccRCC patients. Nomograms have become a frequently used tool for constructing predictive models and have been shown to be more accurate than the conventional staging systems for predicting prognosis.<sup>[19,20]</sup> In recent years, many studies on the prognostic nomograms of ccRCC have been reported.<sup>[21–23]</sup> Also, a previous study has reported a predictive nomogram with immune-associated gene signature for ccRCC patients.<sup>[24]</sup> However, these studies on prognostic nomograms for ccRCC did not involve immune scores which can reflect the extent of immune cell infiltration.

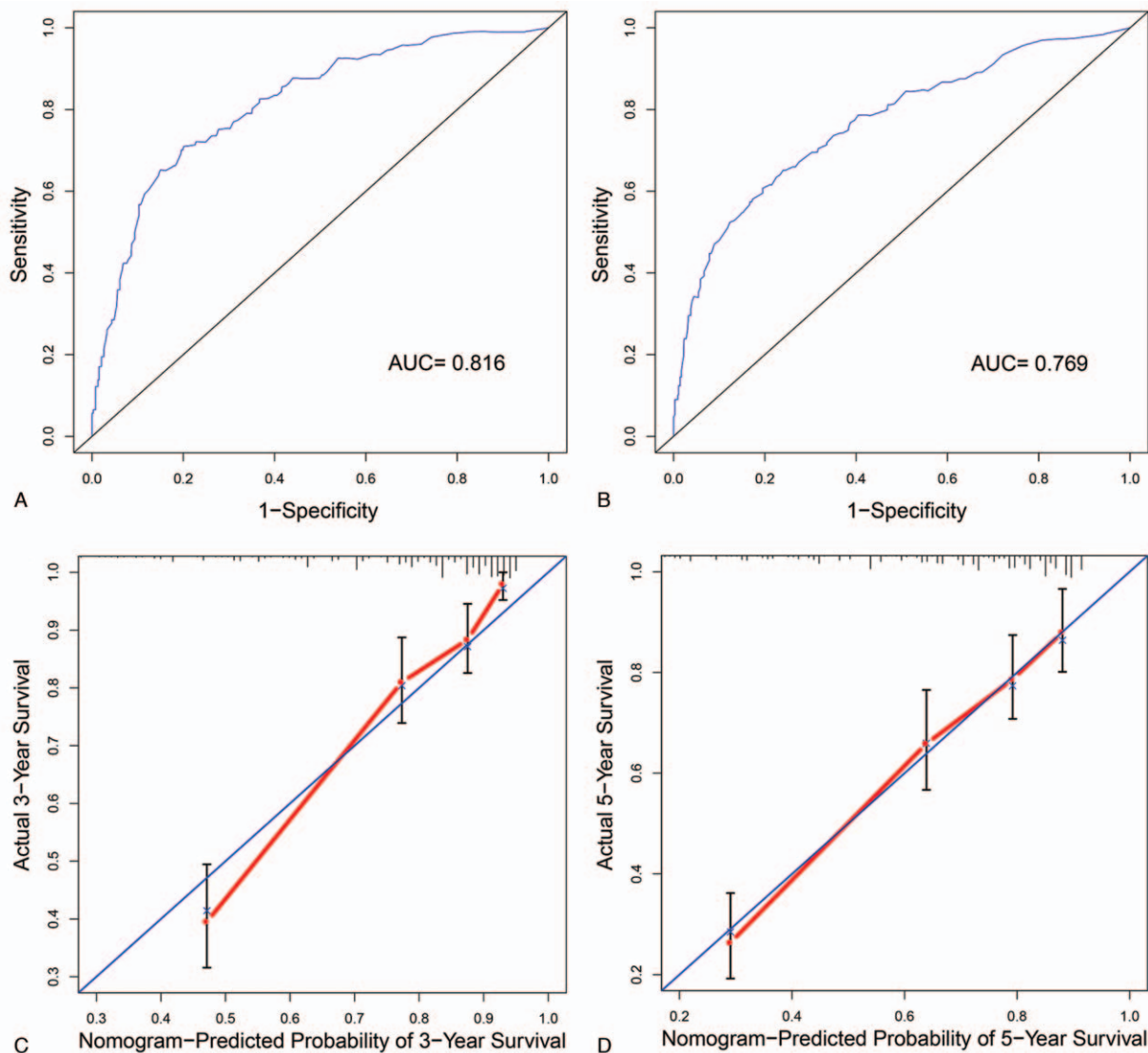


**Figure 3.** Immune scores-based nomogram for predicting overall survival of clear cell renal cell carcinoma patients. For applying the immune scores-based nomogram, every variable axis stands for a risk factor, and a vertical line drawn upward is used to obtain the points of each factor. Total points can be acquired by the sum of 7 variables and could be utilized to predict the survival probabilities of clear cell renal cell carcinoma patients.

The cancer microenvironment is composed of immune cells, stromal cells, and numerous cytokines, etc, and the cells in the microenvironment can promote tumor immune escape, tumor growth, and metastasis.<sup>[2,5]</sup> Previous research proved that several immunological parameters (e.g., programmed death-1, CD8+ tumor-Infiltrating lymphocytes) are associated with poor prognosis of ccRCC.<sup>[26,27]</sup> Besides, a study showed that immunoscore based on immunological analysis has a prognostic value that should be added to the TNM-classification.<sup>[28]</sup> Thus, immune parameters of cancer may contribute to the prognosis and treatment of patients with ccRCC. Furthermore, an immune scores-based nomogram for breast cancer was established, which had good power to predict the OS of breast cancer patients.<sup>[29]</sup> In the present study, we discovered that high-immune scores were significantly related to poor OS time in patients with ccRCC. Two preceding studies also support our findings and revealed that immune scores calculated by ESTIMATE were associated with poor survival.<sup>[7,9]</sup> Generally speaking, activated immune T cells are related to a good prognosis of ccRCC.<sup>[30]</sup> However, B cells increase in late-stage RCC and can reduce the proportion of T cells in cancer microenvironment.<sup>[31]</sup> Moreover, regulatory T cells can also release immunosuppressive cytokines to inhibit tumor immune response, and the overexpression of some chemokine receptors can also promote the growth, invasion, and migration of tumors.<sup>[32]</sup> It is also reported that increased macrophage density is correlated with the high malignant potential of RCC.<sup>[33]</sup> Therefore, previous studies showed that

some of immune cells in cancer microenvironment have the opposite effects, which supports our result. In addition, our result showed that ccRCC patients with low-immune scores tended to be in early T stage or TNM stage, and patients in M1 stage or G3-G4 tended to have high-immune scores. Current literature indicated that the recruitment of CD4+T cells in tumor microenvironment could promote RCC proliferation and regulatory T cells can also inhibit tumor immune responses.<sup>[34,35]</sup> Hu et al reported that higher immune scores may predict the advanced TNM stage,<sup>[36]</sup> which is similar to our results. Additionally, we found that patients with lower immune scores tended to have lower stromal scores. Previous studies suggested that stromal cells also serve an important role in cancer progression.<sup>[37,38]</sup>

Both univariate and multivariate analyses demonstrate that ccRCC patients with low-stromal scores, advanced stage, or left-sided tumors had an increased risk of death. Multivariate Cox analysis of our study suggested that T stage and distant metastasis status may not be the independent factors in ccRCC patients. According to the result of KM survival curves, older age groups had worse survival compared to the youngest age groups. Previous research has shown that the survival probabilities of ccRCC patients decrease as age increases.<sup>[39]</sup> Moreover, the results of this study show that tumor stage and grade could significantly affect the prognosis of ccRCC, which was in line with previous findings.<sup>[40]</sup> Tumors with later stages and grades tend to be more aggressive and have higher malignant potential.



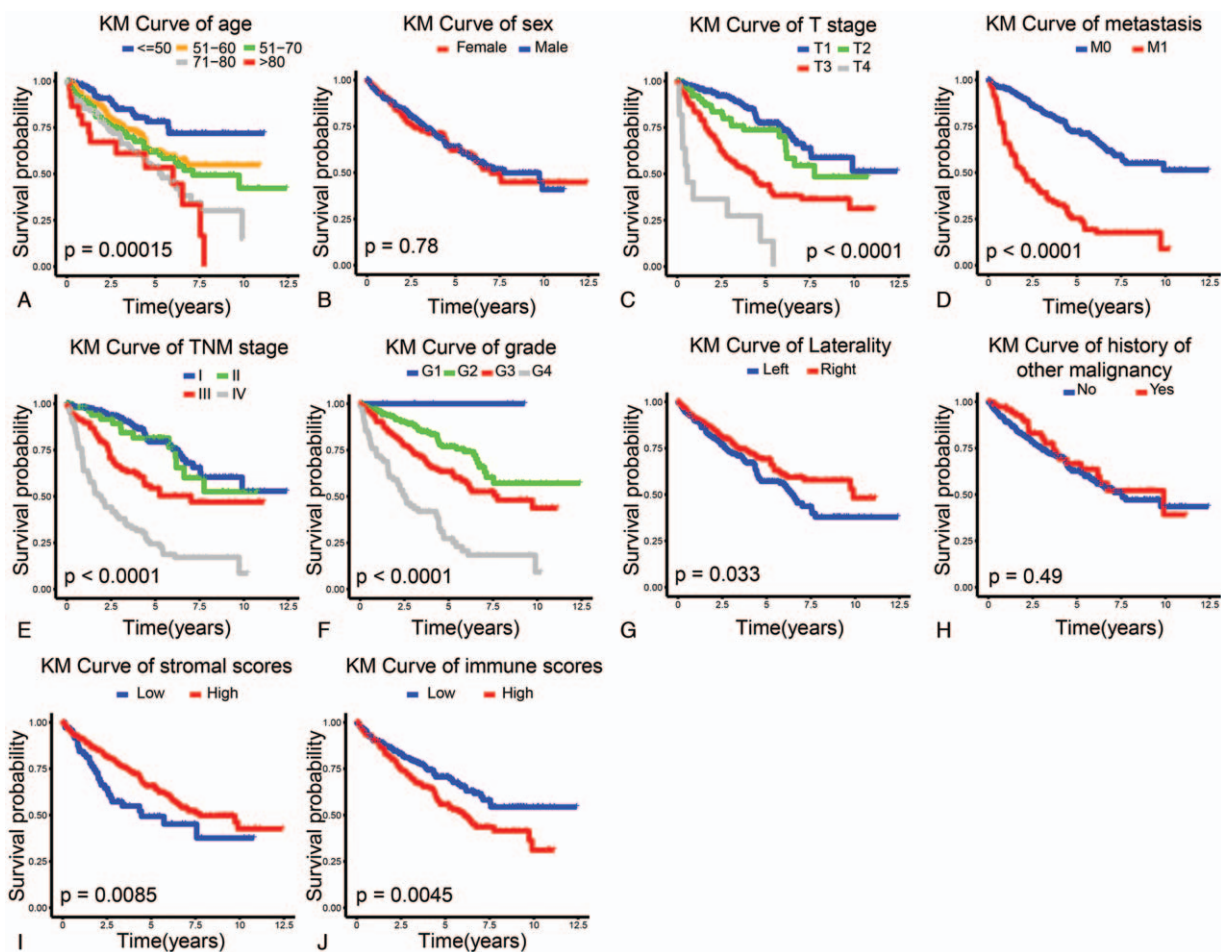
**Figure 4.** The evaluation of the nomogram based on immune scores. (A, B) Receiver operating characteristic curves for the 3- and 5-year overall survival nomogram of clear cell renal cell carcinoma patients. The area under the receiver operating characteristic curves values for 3- and 5-year survival were 0.816 (A) and 0.769 (B), respectively. Calibration plots of the nomogram for (C) 3-year and (D) 5-year overall survival prediction in patients with clear cell renal cell carcinoma.

It has been reported in the literature that right-sided RCC was correlated with better survival than left-sided RCC,<sup>[41]</sup> which also supports our data. Besides, low expression of some genes (e.g., Fer) in stromal cells is related to increased malignant aggressiveness and decreased survival rate in RCC patients.<sup>[42]</sup> As far as we know, this is the first study to construct a nomogram integrated immune scores and clinicopathological factors for predicting the prognosis of ccRCC patients. The area under the curve of ROC curves and c-index value revealed that the immune scores-based nomogram for 3- and 5-year OS had good predictive value. Based on this easy-to-use scoring model, individualized survival prediction could be performed by physicians. Despite the use of multiple approaches to evaluate the correlation between immune scores and prognosis of ccRCC patients, there are several limitations within this study. Firstly, due to fewer ccRCC datasets containing gene expression data that can be applied to obtain immune or stromal scores are

currently available, our findings lacked external verification. Furthermore, due to the absence of some clinical data of patients with ccRCC in TCGA (e.g., prognostic factors including hemoglobin, neoadjuvant chemotherapy), we were unable to include all prognostic factors of ccRCC in the nomogram construction. In addition, the sample sizes were relatively small in some subgroup (e.g., T2 stage, TNM stage II, and G1), which might influence the reliability of the results. Last but not least, other datasets including immune scores should be used to validate our nomogram in future studies, and more immunological parameters are encouraged to improve our model.

## 5. Conclusion

Our research shows that high-immune scores are associated with worse OS in ccRCC patients. In addition, using the TCGA dataset, we have constructed and evaluated a novel nomogram



**Figure 5.** Kaplan–Meier survival curves for overall survival (OS) of patients with Receiver operating characteristic. (A–J) Kaplan–Meier survival curve of clinicopathological factors, stromal scores, and immune scores. Among the 8 clinicopathological parameters, older age (A), later T stage (C), distant metastasis (D), advanced tumor lymph node metastasis stage stage (E), higher tumor grade (F), and left site (G) were associated with worse OS in Receiver operating characteristic patients. Other clinicopathological factors showed no significant difference. High stromal scores (I) and low immune scores (J) were correlated with longer OS time.

for predicting the prognosis of patients with ccRCC. This immune scores-based nomogram may be useful in determining a more accurate OS rate among ccRCC patients and choosing optimal treatment. However, more research is needed to verify the accuracy and reliability of the nomogram.

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### Author contributions

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**Writing – original draft:** Zhulin Wu.

**Writing – review & editing:** Zhulin Wu, Lisheng Peng.

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