ORIGINAL ARTICLE

Preoperative prognostic model for localized and locally advanced renal cell carcinoma: Michinoku Japan Urological Cancer Study Group

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Abstract

Background The Modified International Metastatic Renal Cell Carcinoma Dataset Consortium model (mIMDC) is a pre-operative prognostic model for pT3cN0M0 renal cell carcinoma (RCC). This study aimed to validate the mIMDC and to construct a new model in a localized and locally advanced RCC (LLRCC).

Methods A database was established (the Michinoku Japan Urological Cancer Study Group database) consisting of 79 patients who were clinically diagnosed with LLRCC (cT3b/c/4NanyM0) and underwent radical nephrectomy from December 2007 to May 2018. Using univariable and multivariable analyses, we retrospectively analyzed disease-free survival (DFS) and overall survival (OS) in this database, constructed a new prognostic model according to these results, and estimated the model fit using c-index on the new and mIMDC models.

Results Independent poorer prognostic factors for both DFS and OS include the following: ≥ 1 Eastern Cooperative Oncology Group performance status, 2.0 mg/dL C-reactive protein, and > upper normal limit of white blood cell count. The median DFS in the favorable (no factor), intermediate (one factor), and poor-risk group (two or three factors) was 76.1, 14.3, and 4.0 months, respectively ($P < 0.001$). The 3-year OS in the favorable, intermediate, and poor-risk group were 92%, 44%, and 0%, respectively ($P < 0.001$). The c-indices of the new and mIMDC models were 0.67 and 0.60 for DFS ($P = 0.060$) and 0.74 and 0.63 for OS ($P = 0.012$), respectively.

Conclusion The new preoperative prognostic model in LLRCC can be used in patient care and clinical trials.

Keywords Localized and locally advanced renal cell carcinoma · Nephrectomy · Overall survival · Prognostic model · Recurrence-free survival · Renal cell carcinoma

Introduction

Nephrectomy is the gold standard treatment for localized renal cell carcinoma (RCC). After nephrectomy, the recurrence rate in localized and locally advanced RCC (LLRCC) is higher (42% in pT3 and 47% in pT4) than in non-invasive RCC (5% in pT1a, 15% in pT1b, and 35% in pT2) [1]. Therefore, the benefit of adjuvant therapy has been extensively studied in LLRCC. However, currently, the efficacy of adjuvant therapy is controversial [2]. No statistically significant differences in overall survival (OS) have been demonstrated in several randomized trials of molecular targeted agents in the adjuvant setting [3–6]. More recently, pembrolizumab, an immune checkpoint inhibitor (ICI), showed a short-time

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benefit in disease-free survival (DFS) (hazard ratio [HR] 0.63; 95% confidence interval [95% CI], 0.50 to 0.80) and OS (HR 0.52, 95% CI 0.31 to 0.86) [7]. However, the long-term follow-up results were not reported in this study, and other ICI adjuvant regimens, such as nivolumab plus ipilimumab and atezolizumab, did not exhibit any statistical differences compared with placebo for either DFS or OS [8, 9].

In addition, the 30-day mortality for radical nephrectomy with vena cava tumor thrombus (cT3b/c RCC) was reported to be approximately 1.5–10%, and the complication rates were approximately 18–47%, which gradually increased depending on the thrombus level [10]. Considering the uncertain benefit of adjuvant treatment and the high risk of nephrectomy, clinical trials in the neoadjuvant setting for LLRCC are warranted. However, as postoperative data are usually utilized to evaluate for recurrence risk, information

on preoperative prognostic factors for recurrence is limited, and the appropriate patients for inclusion in neoadjuvant therapy trials remain unclear. A previous report showed that the Modified International Metastatic Renal Cell Carcinoma Dataset Consortium (mIMDC) model predicts OS in pT3c RCC, whose prognostic factors are anemia, neutrophilia, thrombophilia, hypercalcemia, and Karnofsky performance status (PS) < 80. However, no validation has been conducted for this classification [11]. In this study, a new prognostic model was constructed and mIMDC in LLRCC was validated.

Patients and methods

A database was established (the Michinoku Japan Urological Cancer Study Group database) consisting of 79 patients with clinically diagnosed LLRCC (cT3b/c/4NanyM0) and who underwent radical nephrectomy at Hirosaki University Graduate School of Medicine, University of Tsukuba Graduate School of Medicine, Akita University Graduate School of Medicine, Yamagata University Faculty of Medicine, Iwate Medical University School of Medicine, Fukushima Medical University School of Medicine, Miyagi Cancer Center, and Tohoku University School of Medicine from December 2007 to May 2018. The last follow-up date was September 2020.

This study aimed to construct new models for predicting DFS and OS in LLRCC, and to evaluate the model fit of the new and mIMDC models in LLRCC.

First, univariable analyses were used to compare DFS and clinical factors. From the date of nephrectomy to recurrence or last-follow-up, DFS was estimated using the Kaplan–Meier method. Univariable analyses were performed using the log-rank test with a significance level of 0.05. The clinical factors investigated included sex, Eastern Cooperative Oncology Group PS (ECOG PS) (ECOG PS 0 or ≥ 1), cT (3b, 3c, or 4), cN (0 or 1), serum albumin level (Alb) (≥ lower limit of normal [LLN] or < LLN), serum alkaline phosphatase level (≤ upper limit of normal [ULN] or > ULN), serum calcium level (Ca) (≤ ULN or > ULN), corrected Ca (Ca − 0.707*[Alb–3.4]) (≤ ULN or > ULN), C-reactive protein (CRP) (≥ 2.0 mg/dL or > 2.0 mg/dL), hemoglobin (Hb) (≥ LLN or < LLN), serum lactate dehydrogenase level (≤ 1.5*ULN or > 1.5*ULN), blood white blood cell count (WBC) (≤ ULN or > ULN), blood neutrophil count (Neut) (≤ ULN or > ULN), blood lymphocyte count (Lym) (≥ LLN or < LLN), Neut to Lym ratio (NLR) (≤ 5.0 or > 5.0), blood platelet count (≤ ULN or > ULN), neoadjuvant treatment (yes or no), and adjuvant treatment (yes or no). Using a software X-Tile version 3.6.1 (http://tissuearray.org), cutoff points for CRP and NLR were determined through the greatest statistical difference measured. Data were collected prior to RCC treatment. If patients underwent treatment with neoadjuvant systemic therapy, data were collected before systemic therapy.

Factors that were significantly correlated with a worse DFS in the univariable analyses were then included in the multivariable analysis. Using a stepwise method, multivariable analysis using the Cox proportional model was performed with a significance level of < 0.05 for the exclusion of variables. A new prognostic model was then created according to the estimated values calculated in the multivariable analysis.

The c-index was then calculated with 1000 bootstrap on the new and mIMDC models. Using the c-index with 1000 bootstrap samples for patients with complete data, discrimination between models was assessed to calculate the prognostic models.

OS was also analyzed using the same steps as for DFS. OS was estimated using the Kaplan–Meier method from the date of nephrectomy until death or last-follow-up.

The statistical software package R version 3.6.1 was used for the statistical analyses (https://cran.r-project.org). The "rms" library of R was used for the evaluation of c-indices, and the "compareC" library of R was used for the correlations of c-indices. The Ethics Committee of Yamagata University Faculty of Medicine approved this study (approval no. 2019-126). The methods were performed in accordance with the approved guidelines. Informed consent to participate in this study was waived by the ethics committee and the national guidelines.

Results

Patient characteristics

Table 1 shows the patient characteristics. The median age and follow-up period were 66 (range 39–85) years and 24.6 (95% CI 9.1–55.7) months, respectively. The number (%) of cT3b, cT3c, cT4, cN0, and cN1 was 64 (81.0%), 7 (8.9), 8 (10.1), 70 (89.7), and 8 (10.3), respectively. A total of 44 recurrences (55.7%) and 4 deaths without recurrence (5.1%) were documented. The median DFS was 27.0 (95% CI 11.2–42.3) months. The 1-, 3-, and 5-year survival rates were 85.9%, 63.5%, and 53.6%, respectively. Twenty (25.3%) and seven (8.9%) patients received neoadjuvant and adjuvant systemic therapy around nephrectomy, respectively. All neoadjuvant treatments were molecular targeted agents (Supplementary Table 1), while adjuvant treatments include cytokines and molecular targeted agents. Three patients had unknown adjuvant therapies; however, it is unlikely that ICIs were used based on the dates of surgery (Supplementary Table 2). On the last day of follow-up, 50 (63.3%) patients remained alive, and six (7.6%) patients died of causes other than RCC. No patient died within 30 days of nephrectomy.

Table 1 Patient characteristics

Number	79
Age [Median (range), years]	66 (39–85)
Sex	
Male, *n* (%)	55 (69.6)
Female, *n* (%)	24 (30.4)
cT	
3b, *n* (%)	64 (81.0)
3c, *n* (%)	7 (8.9)
4, *n* (%)	8 (10.1)
cN	
0, *n* (%)	70 (89.7)
1, *n* (%)	8 (10.3)
ECOG PS	
0, *n* (%)	59 (74.7)
1, *n* (%)	15 (19.0)
2, *n* (%)	3 (3.8)
3, *n* (%)	1 (1.3)
4, *n* (%)	1 (1.3)
Neoadjuvant treatment	
Yes, *n* (%)	20 (25.3)
No, *n* (%)	59 (74.7)
Adjuvant treatment	
Yes, *n* (%)	7 (8.9)
No, *n* (%)	72 (91.1)
Follow-up duration [Median (IQR), months]	24.6 (9.1–55.7)
Disease-free survival [Median (95% CI), months]	27.0 (11.0–42.3)
Overall survival	
1-year, %	85.9
3-year, %	63.5
5-year, %	53.6
Outcome	
Alive, *n* (%)	50 (63.3)
Death due to renal cell carcinoma, *n* (%)	23 (29.1)
Non-renal cell carcinoma related death, *n* (%)	6 (7.6)
Death within 30 days after surgery, *n*	0

Preoperative clinical parameters for predicting DFS

Univariable analyses showed statistical differences in ECOG PS, CRP, WBC, Neut, and NLR (Supplementary Table 3). Therefore, a multivariable analysis was performed using ECOG PS, CRP, WBC, Neut, and NLR. In the multivariable analysis, there were three independent worse predictors of DFS before treatment (≥ 1 ECOG PS, > 2.0 mg/dL CRP, and > ULN of WBC) (Table 2 and Supplementary Table 3).

The patients were categorized into three risk groups according to three poor prognostic factors as follows: favorable-risk group, no risk factors ($n = 41$, 51.9%); intermediate-risk group, one risk factor ($n = 27$, 34.2%); and poor-risk

group, two or three risk factors ($n = 11$, 13.9%). In our new model, the median DFS (95% CI) in the favorable, intermediate, and poor-risk groups were 76.1 (34.1–not applicable [NA]) months, 14.3 (9.1–35.1) months, and 4.0 (3.1–12.9) months, respectively ($P < 0.001$) (Fig. 1a). Besides, in the mIMDC model, the median DFS (95% CI) in the favorable ($n = 20$, 26.3%), intermediate ($n = 43$, 56.6%), and poor-risk groups ($n = 13$, 17.1%) were 55.0 (9.9–NA) months, 34.1 (14.3–58.0) months, and 4.0 (3.1–18.2) months, respectively ($P < 0.001$) (Fig. 1b). The new model predicted DFS relatively more accurately than the mIMDC model (c-index; 0.67 vs. 0.60, $P = 0.060$).

Preoperative clinical parameters for predicting OS

In the univariable analyses, statistical differences in ECOG PS, Alb, CRP, WBC, Neut, and NLR were found (Supplementary Table 4). Therefore, using ECOG PS, Alb, CRP, WBC, Neut, and NLR, a multivariable analysis was performed. The multivariable analysis showed three independent worse predictors of OS prior to treatment (≥ 1 ECOG PS, > 2.0 mg/dL CRP, and > ULN of WBC). These factors were similar for DFS (Table 3 and Supplementary Table 4). Therefore, to predict OS, the same model was used as that of DFS.

In the new model, 3-year OS rates in the favorable (no risk factors), intermediate (one risk factor), and poor-risk groups (two or three risk factors) were 92%, 44%, and 0%, respectively ($P < 0.001$, Fig. 2a). In the modified IMDC model, the 3-year OS rates in the favorable, intermediate, and poor-risk group were 75%, 72%, and 15%, respectively ($P < 0.001$, Fig. 2b). The c-index of the new model predicted OS more accurately than the modified IMDC model (c-index; 0.74 vs. 0.63, $P = 0.012$).

Discussion

In this study, a new prognostic model was constructed to predict DFS and OS in LLRCC. The new model is calculated by the number of prognostic factors: ≥ 1 ECOG PS, > 2.0 mg/dL CRP, and > ULN of WBC. The median DFS (95% CI) and 3-year OS in the favorable (no risk factors), intermediate (one risk factor), and poor (two or three risk factors) risk groups were 76.1 (34.1, NA) months and 92%, 14.3 (9.1–35.1) months and 44%, and 4.0 (3.1–12.9) months and 0%, respectively (Figs. 1a and 2a). To date, preoperative prognostic models for LLRCC have been limited. The Guy's Hospital group showed that the IMDC risk score, commonly used for metastatic RCC patients, could also be applied to patients with localized pT3c [11]. We validated this mIMDC

Table 2 Multivariable analysis for predicting disease-free survival

Variable	n	Median DFS, months	95% CI, months	Multivariate analysis		
				HR	95% CI	P
ECOG PS						
0	50	42.3	14.3–101.8			
>0	20	11.9	3.8–26.0	2.28	1.16–4.47	0.017
CRP						
Continuous						
≤2.0 mg/dL	54	42.3	19.3–101.8			
>2.0 mg/dL	25	9.6	3.8–22.2	2.35	1.29–4.28	0.005
WBC						
≤ULN	72	35.2	19.3–58.0	5.21	2.08–13.1	<0.001
>ULN	7	3.8	2.2–12.0	5.21	2.08–13.1	<0.001

ECOG PS Eastern Cooperative Oncology Group Performance Status, *CRP* C-reactive protein, *WBC* white blood cell, *DFS* disease-free survival, *95% CI* 95% confidence interval, *HR* hazard ratio
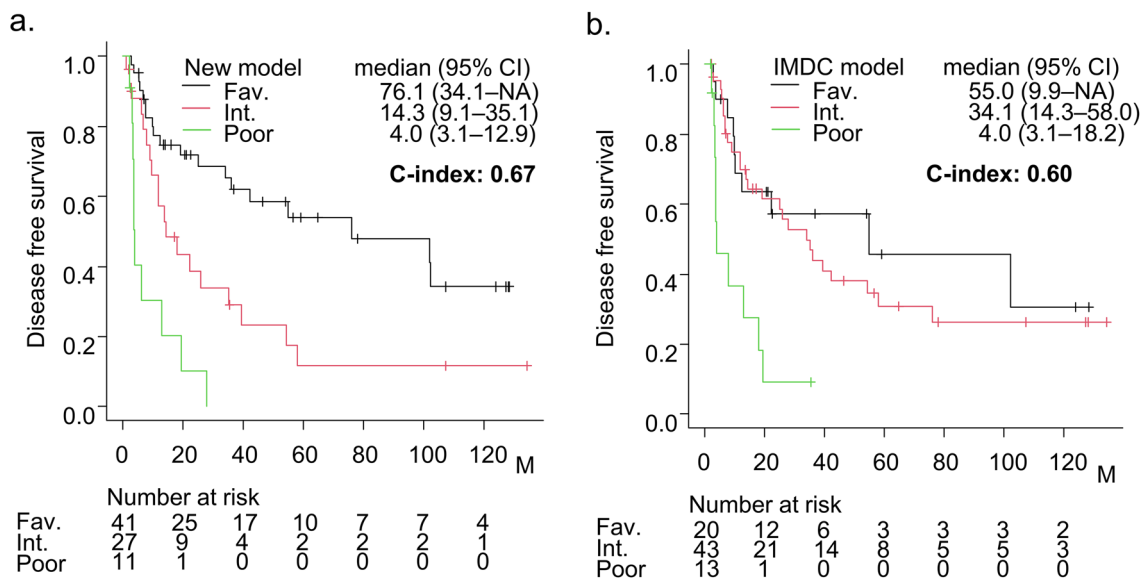
Fig. 1 Disease-free survival in each risk group of the new model (**A**) and the mIMDC model (**B**). *M* months; *95% CI* 95% confidence interval; *mIMDC* Modified International Metastatic Renal Cell Carcinoma Database Consortium, *Fav* favorable, *Int* intermediate

model for localized cT3b/3c/4 RCC and demonstrated its applicability (c-index = 0.60 and 0.63 for DFS and OS, respectively) (Figs. 1b and 2b). Besides, the c-index of the new model was 0.67 for DFS and 0.74 for OS. In the present study, although an internal validation was not conducted owing to the small cohort and the requirement for external validation studies to confirm the utility of the new model, DFS and OS were more accurately predicted by the new model in our cohort ($P = 0.060$ in DFS and $P = 0.012$ in OS).

Majority of the previous prognostic models for LLRCC was calculated using postoperative factors including pathological features, and a high pathological T stage and grade are generally worse factors for predicting DFS and OS

[12–18]. To accurately predict DFS or cancer-specific survival with a c-index of 0.74–0.84, an external validation has been conducted for these models [19]. In fact, patients with high stage and/or high grade RCC were included in the adjuvant therapy trials [3–9]. However, since these models include pathological parameters, they cannot be used before nephrectomy. The new model is deemed suitable for neoadjuvant trials and is a factor in deciding whether to undergo neoadjuvant treatment in a clinical setting, as it is constructed from preoperative factors and has a high accuracy despite exclusion of pathological parameters.

In this study, all prognostic factors identified (≥ 1 ECOG PS, > 2.0 mg/dL CRP, and > ULN WBC) are related to

Table 3 Multivariable analysis for predicting overall survival

Variable	n	Median OS	95% CI	Multivariate analysis		
				HR	95% CI	P
ECOG PS						
0	59	141.6	54.4–NA			
>0	20	26.0	7.8–NA	2.48	1.07–5.77	0.035
CRP						
≤2.0 mg/dL	54	141.6	76.1–NA			
>2.0 mg/dL	25	22.3	8.0–35.0	4.37	1.98–9.65	<0.001
WBC						
≤ULN	72	141.6	54.4–NA			
>ULN	7	16.7	2.3–NA	4.75	1.82–12.39	0.001

ECOG PS Eastern Cooperative Oncology Group Performance Status, *CRP* C-reactive protein, *WBC* white blood cell, *OS* overall survival, *95% CI* 95% confidence interval, *HR* hazard ratio, *NA* not applicable
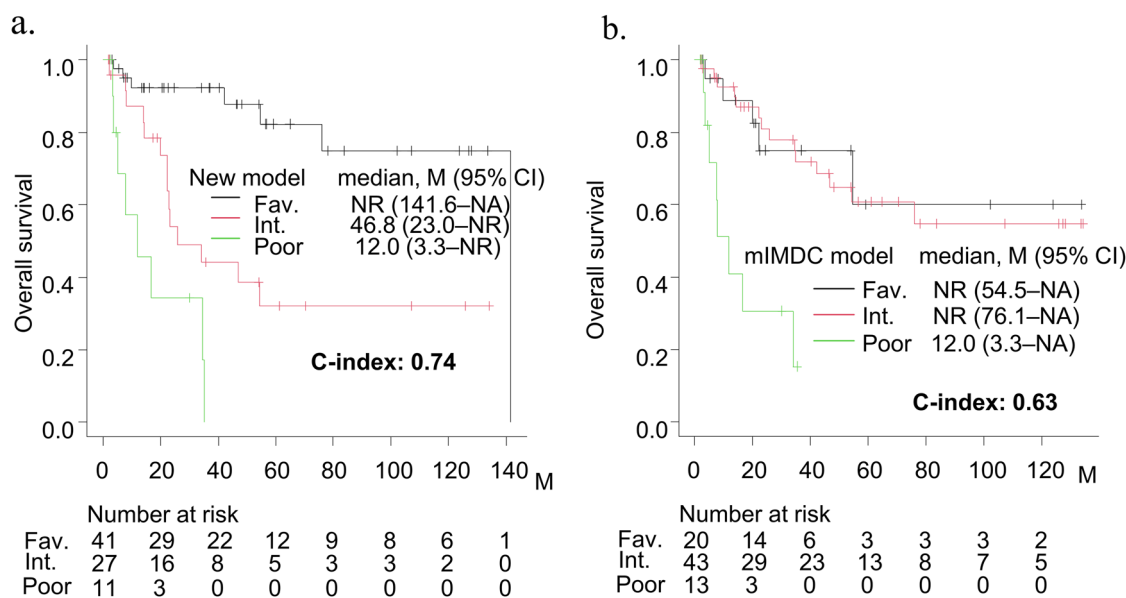
Fig. 2 Overall survival in each risk group of the new model (**A**) and the mIMDC model (**B**). *M* months, *95% CI* 95% confidence interval, *mIMDC* Modified International Metastatic Renal Cell Carcinoma Database Consortium, *Fav* favorable, *Int* intermediate

systemic inflammation (Tables 2 and 3). For most cancers, systemic inflammation is reported to be a poor prognostic factor. PS has been associated with interleukin-6, an inflammatory cytokine, and poor survival in patients with advanced cancer [20, 21]. One of the IMDC factors in RCC is PS [22]. In addition, numerous previous reports showed that CRP was a prognostic factor in preoperative and metastatic stages in RCC [23–29]. WBC was an independent risk factor, but Neut and NLR were not included in this study. Previous reports showed that Neut and NLR were risk factors in the preoperative or metastatic stage [22, 24]. This discrepancy may be due to the small number of cases and the missing cases in the data for Neut in this study.

This study has several limitations. First, it was a retrospective study with a small sample size. Therefore, an internal validation could not be performed. Second, this study lacked external validation. Third, all patients were Japanese, which may hinder generalizability of the results. Third, approximately, a quarter of the patients received peri-operative systemic treatments, which could affect DFS and OS. However, all the agents used as neoadjuvant and adjuvant therapies were cytokines or molecular targeted agents. These regimens have not shown to improve OS in previous clinical trials. Finally, the treatment strategies were revised during the study period. Some patients could not undergo ICI because of the pre-ICI era, which could have a strong impact on OS.

In conclusion, ≥1 ECOG PS, >2.0 mg/dL CRP, and >ULN WBC are preoperative prognostic factors in

LLRCC. According to these factors, the new model can accurately predict DFS and OS.

Declarations

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