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Original Article

External validation of the albumin, C-reactive protein and lactate dehydrogenase model in patients with metastatic renal cell carcinoma receiving second-line axitinib therapy in a Japanese multi-center cohort

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Abstract

Purpose: To externally validate the utility of the albumin, C-reactive protein and lactate dehydrogenase model to predict the overall survival of previously treated metastatic renal cell carcinoma patients.

Patients and methods: The ability of the albumin, C-reactive protein and lactate dehydrogenase model to predict overall survival was validated and compared with those of other prognostication models using data from 421 metastatic renal cell carcinoma patients receiving second-line axitinib therapy at 36 hospitals belonging to the Japan Urologic Oncology Group.

Results: The following factors in this cohort were independently associated with poor overall survival in a multivariate analysis: a low Karnofsky performance status, <1 year from diagnosis to targeted therapy, a high neutrophil count, and low albumin, elevated C-reactive protein, and

elevated lactate dehydrogenase, and the Japan Urologic Oncology Group model was newly developed based on the presence/absence of these independent factors. In this cohort, 151 (35.9%), 125 (27.7%) and 145 (34.4%) patients were classified into the favorable, intermediate and poor risk groups, respectively, according to the albumin, C-reactive protein and lactate dehydrogenase model; however, the proportions of patients in the intermediate risk group stratified by the Japan Urologic Oncology Group, Memorial Sloan Kettering Cancer Center and International Metastatic Renal Cell Carcinoma Database Consortium models were >50%. The superiority of the albumin, C-reactive protein and lactate dehydrogenase model to the Memorial Sloan Kettering Cancer Center and International Metastatic Renal Cell Carcinoma Database Consortium models, but not the Japan Urologic Oncology Group model, was demonstrated by multiple statistical analyses.

Conclusions: The utility of the albumin, C-reactive protein and lactate dehydrogenase model as a simple and objective prognostication tool was successfully validated using data from 421 metastatic renal cell carcinoma patients receiving second-line axitinib.

Key words: previously treated metastatic renal cell carcinoma, targeted therapy, axitinib, prognostic model, overall survival, external validation, concordance index, decision curve analysis

Introduction

Systemic therapy for metastatic renal cell carcinoma (mRCC) has markedly advanced since the introduction of molecular targeted agents, including vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors, resulting in significant improvements in the prognosis of mRCC patients (1). In addition, with the advent and subsequent approval of immune check point inhibitors, such as those targeting programmed death (PD)-1, PD-ligand 1 and cytotoxic T-lymphocyte antigen 4, mRCC patients benefit further from these novel agents (2). However, due to the increasing complexity of therapeutic strategies with the availability of multiple efficacious agents, difficulties are associated with the selection of optimal treatments for mRCC patients in real-world clinical practice, particularly those for previously treated patients (3).

To date, a number of studies have advocated various types of prognostication models consisting of potential prognostic parameters for mRCC patients (4,5), and these are currently regarded as useful tools for facilitating the selection of appropriate agents for each mRCC patient (4,6–9). Two major model systems, the Memorial Sloan Kettering Cancer Center (MSKCC) model for previously treated patients and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, have commonly been used for the prognostication of mRCC patients who failed first-line therapy (8,9). However, a number of limitations have been associated with the application of these two models to current cohorts of mRCC patients in the second-line setting, such as the higher proportion of patients receiving first-line cytokine therapy in the study cohort of the MSKCC second-line model (8) and the more direct application of the IMDC model for treatment-naïve patients (7) to that for previously treated patients (9).

Based on these findings, recent studies reported novel risk stratification systems for mRCC patients after the failure of first-line therapy (10–12). We also demonstrated the usefulness of the albumin [Alb], C-reactive protein [CRP] and lactate dehydrogenase [LDH] (ACL) model as a novel prognostication tool for mRCC patients previously treated with first-line molecular targeted agents (13); however, this was established using data obtained from a small number of patients receiving several second-line agents, and the validation of this model using external data has not yet been conducted. Therefore, we herein externally validated the usefulness of the ACL model using data from 421 mRCC patients receiving axitinib as second-line therapy at 36 institutions belonging to the Japan Urologic Oncology Group (JUOG). We subsequently developed a novel prognostication model called the JUOG model based on the data of these 421 mRCC patients, and performed comparative assessments for the abilities of four systems, namely, the ACL, JUOG, MSKCC (8) and IMDC (9) models, to assess the prognosis of mRCC patients in a second-line setting.

Patients and methods

Patients

Clinicopathological data were retrospectively obtained from 526 mRCC patients who received second-line axitinib therapy after treatment with a TKI between January 2012 and February 2019 at 36 hospitals belonging to the JUOG. After the exclusion of 43 patients without a pathological diagnosis, 49 receiving axitinib for <4 weeks and 13 lacking a complete data set from these 526, 421 were ultimately included in the present study.

Administration of targeted agents

In this series, one of the three TKIs currently available in Japanese clinical practice, pazopanib, sorafenib and sunitinib, was administered to each patient as first-line therapy, and axitinib therapy was subsequently performed in a second-line setting according to standard dosing schedules, as previously reported (14–17). However, modifications to the dosing schedule based on the severity of adverse events in each patient were permitted.

Evaluation

All data assessed in the present study were obtained from the medical records of each patient. As baseline examinations at the initiation of second-line axitinib therapy, the performance status (PS) was evaluated by the Eastern Cooperative Oncology Group (ECOG) PS, and standard clinical testing methods were used to measure laboratory data. Before the administration of second-line axitinib, the following radiological examinations were conducted for all patients: computed tomography (CT) of the brain, chest and abdomen and/or

a radionuclide bone scan. During treatment with axitinib, changes in each tumor size were generally measured by CT every 12 weeks. OS after the initiation of treatment with axitinib was defined as the duration between the introduction of axitinib and data on death from any cause or censorship on the day of the last follow-up visit. In this series, due to the absence of data on Karnofsky PS (KPS), ECOG PS ≥ 2 was assumed as KPS $< 80\%$ for risk classification.

Statistical analysis

The Kaplan–Meier method was used to calculate OS rates, and the prognostic significance of several factors was evaluated using uni- and multi-variate Cox's proportional hazards models. Only factors corresponding to P values < 0.15 in the univariate analysis were included in the multivariate analysis with backward stepwise selection as previously described (7).

The ability of the four prognostication models to predict OS was compared with the following statistical analyses: calibration curves were plotted to quantify how close a predicted estimate was to the real probability (18); Harrell's concordance index (C-index), relevant to the area under the receiver operating characteristic curve (AUC), was calculated (19); chronological changes in the AUC were analyzed using 5-fold cross validation to decrease an over fit bias (20); and the decision curve analysis (DCA) reported by Vickers et al. was performed to assess the net benefit for clinical utility (21).

In the present study, P values < 0.05 were considered to be significant. All statistical analyses were performed with R software V.4.0.0 (http://www.r-project.org), except for DCA, which was performed using programs available at https://www.mskcc.org/departments/epidemiology-biostatistics/biostatistics/decision-curve-analysis.

Results

Patient characteristics and prognostic outcomes

Table 1 shows the clinicopathological characteristics of the 421 patients included in the present study. Of these, 214 (50.8%) patients had metastatic disease at diagnosis. In this series, pazopanib, sorafenib or sunitinib was introduced as the first-line targeted therapy, and second-line therapy with axitinib was subsequently conducted for all 421 patients.

The median follow-up period after the initiation of second-line axitinib in the 421 patients was 23.0 months (interquartile range, 11.0–35.0 months). During the follow-up period, death from any cause occurred in 230 patients (54.6%). The median duration of OS was 30 months (95% confidence interval [CI], 26–37), and 1-, 2- and 3-year OS rates were 0.78 (95% CI, 0.73–0.81), 0.56% (95% CI, 0.51–0.61) and 0.46% (95% CI, 0.41–0.51), respectively.

Prognostic outcomes and building of a novel prognostication model

To identify parameters associated with OS after the initiation of second-line axitinib therapy in the 421 patients, several potential factors were examined by uni- and multi-variate Cox's regression analyses (Table 2). The univariate analysis showed that OS correlated with the time from first- to second-line therapy, ECOG PS, the time from diagnosis to targeted therapy, hemoglobin (Hb), corrected calcium, the neutrophil count, platelet count, Alb, CRP and LDH. Among these factors, the multivariate analysis identified ECOG PS, the time from diagnosis to targeted therapy, the neutrophil count, Alb, CRP and LDH as independent predictors of OS.

Table 1. Patient characteristics

	$N = 421$
Gender, Male (%)	329 (78.2)
Age at start of second-line therapy, year Median (IQR)	67 (60–73)
Histology, Clear cell renal cell carcinoma (%)	371 (88.1)
Previous nephrectomy, no (%)	42 (10.0)
Metastatic sites (%)	
Brain	20 (64.8)
Lung	290 (68.9)
Liver	69 (16.4)
Bone	136 (32.3)
Type of first-line targeted therapy (%)	
Sunitinib	305 (72.5)
Sorafenib	83 (19.7)
Pazopanib	33 (7.8)
<1 year from first- to second-line targeted therapy (%)	278 (66.0)
KPS < 80% (%)	39 (9.3)
<1 year from diagnosis to targeted treatment (%)	208 (49.4)
Hb concentration < lower limit of normal (%)	63 (80.1)
Corrected Ca concentration > 10 mg/dL (%)	73 (17.3)
Neutrophil count > upper limit of normal (%)	27 (6.4)
Platelet count > upper limit of normal (%)	62 (14.7)
Alb concentration ≤ 3.5 g/dL (%)	170 (40.4)
CRP level > 0.5 mg/dL (%)	234 (55.6)
LDH concentration > 1.5 × upper limit of normal (%)	31 (7.36)

IQR, interquartile range; KPS, Karnofsky performance status; Hb, hemoglobin; Ca, calcium; Alb, albumin; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Based on the results of Cox's regression analyses, a novel prognostication model, called the JUOG model, was developed by defining six parameters as risk factors for poor OS, including high ECOG PS (≥2), <1 year from diagnosis to targeted treatment, an elevated neutrophil count (upper limit of normal), low Alb (≤3.5 g/dL), elevated CRP (>0.5 mg/dL) and elevated LDH (>1.5 × upper limit of normal). In this model, patients were stratified into the following three groups according to the presence/absence of these independent risk factors: a favorable risk group, patients without risk factors; an intermediate risk group, patients with one or two risk factors; and a poor risk group, patients with ≥three risk factors.

Risk stratifications using ACL, JUOG, MSKCC and IMDC models

Table 3 summarizes the outcomes of risk stratifications, including the number of deaths and median OS, by the four prognostication models, the AUC, JUOG, MSKCC and IMDC models. The ACL model, but not the other three models, showed a comparatively even distribution of the 421 patients into three risk groups; the proportions of patients classified into the intermediate risk group by the JUOG, MSKCC and IMDC models were >50%; however, significant differences were observed in OS among the three risk groups in all four prognostication model systems (Fig. 1).

Comparison of performance among ACL, JUOG, MSKCC and IMDC models

To quantify how close a predicted estimate was to the real probability for surviving 30 months after the initiation of second-line axitinib therapy by each model, we plotted calibration curves using 5-fold

Table 2. Univariate and multivariate analyses of prognostic factors following the initiation of axitinib

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender, Male	0.692 (0.68–1.23)	0.61	–	–
Age at start of second-line therapy ≥70 years	1.02 (0.78–1.33)	0.9	–	–
≥1 year from first to second-line targeted therapy	1.51 (1.14–2.01)	0.004	–	–
KPS < 80%	3.34 (2.31–4.83)	<0.001	2.32 (1.57–3.41)	<0.001
<1 year from diagnosis to targeted treatment	2.05 (1.57–2.66)	<0.001	1.88 (1.43–2.46)	<0.001
Hb concentration < lower limit of normal	1.87 (1.28–2.71)	0.001	–	–
Corrected Ca concentration > upper limit of normal	1.60 (1.17–2.20)	0.003	–	–
Neutrophil count > upper limit of normal	2.16 (1.38–3.39)	<0.001	2.23 (1.39–3.56)	<0.001
Platelet count > upper limit of normal	1.09 (0.75–1.59)	0.65	–	–
Alb concentration ≤ 3.5 g/dL	2.86 (2.20–3.71)	<0.001	1.92 (1.42–2.59)	<0.001
CRP level > 0.5 mg/dL	2.30 (1.75–3.02)	<0.001	1.40 (1.02–1.90)	0.034
LDH concentration > 1.5 × upper limit of normal	1.94 (1.27–3.00)	0.002	1.69 (1.10–2.61)	0.017

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; Hb, hemoglobin; Ca, calcium; Alb, albumin; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 3. Prognostic risk stratification by each model following the initiation of axitinib

	N (%)	Number of deaths (%)	Median OS in months (95% CI)	HR (95% CI)
The ACL model				
Favorable	151 (35.9)	57 (37.7)	50 (42-NR)	1 (ref)
Intermediate	125 (29.7)	61 (48.8)	30 (23–52)	1.57 (1.10–2.26)
Poor	145 (34.4)	112 (77.2)	14 (12–17)	3.70 (2.68–5.11)
The JUOG model				
Favorable	88 (20.9)	25 (28.4)	NR (50-NR)	1 (ref)
Intermediate	217 (51.5)	109 (50.2)	37 (27–50)	2.29 (1.48–3.54)
Poor	116 (27.6)	96 (82.8)	12 (8–14)	7.09 (4.45–11.1)
The MSKCC model				
Favorable	81 (19.2)	30 (37)	44 (37-NR)	1 (ref)
Intermediate	249 (59.1)	129 (51.8)	34 (25–50)	1.54 (1.03–2.29)
Poor	91 (21.6)	71 (78.0))	14 (12–25)	3.30 (2.15–5.07)
The IMDC model				
Favorable	34 (8.1)	12 (35.3)	44 (37-NR)	1 (ref)
Intermediate	297 (70.5)	151 (50.8)	37 (2–50)	1.78 (0.99–3.20)
Poor	90 (21.3)	67 (74.4)	14 (10–19)	4.14 2.23–7.66

OS, overall survival; HR, hazard ratio; CI, confidence interval; ACL (albumin, C-reactive protein, and lactate dehydrogenase); JUOG, Japan Urologic Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

cross validation from data sets of the 421 patients. The ACL and JUOG models had better predictive accuracies between estimated probabilities and actual outcomes than the MSKCC and IMDC models (Fig. 2).

The C-index in each model was then calculated to analyze the ability to predict OS following the initiation of second-line treatment with axitinib. The C-indexes of the ACL, JUOG, MSKCC and IMDC models were 0.670 (95% CI, 0.602–0.739), 0.696 (95% CI, 0.634–0.758), 0.611 (95% CI, 0.541–0.680) and 0.609 (95% CI, 0.547–0.670), respectively. The JUOG model was shown to be the most accurate with significant differences from the ACL, MSKCC and IMDC models ($P = 0.026$, <0.001 and < 0.001, respectively), while the predictive ability of the ACL model was significantly superior to those of the MSKCC and IMDC models ($P = 0.003$ and 0.012, respectively).

We also evaluated adjusted C-indexes and time-dependent AUCs at 9 points during the follow-up period with 5-fold cross validation to represent the bias-corrected performance of the four prognostication models. The adjusted C-indexes of the ACL, JUOG, MSKCC and IMDC models were 0.672, 0.694, 0.606 and 0.607, respectively. Changes in adjusted time-dependent AUCs at 9 points during the follow-up period are shown in Figure 3. At any time point, the ACL and JUOG models had higher accuracy than the MSKCC and IMDC models.

DCA was conducted to evaluate the net benefit of the models for predicting OS 1, 2 and 3 years after the introduction of second-line axitinib. Each model was useful between threshold probabilities of 0.12 and 0.36 at 1 year, 0.27 and 0.65 at 2 years, and 0.38 and 0.76 at 3 years (Fig. 4). In addition, the ACL and JUOG models showed a better net benefit in a wide range of threshold probabilities 1, 2 and

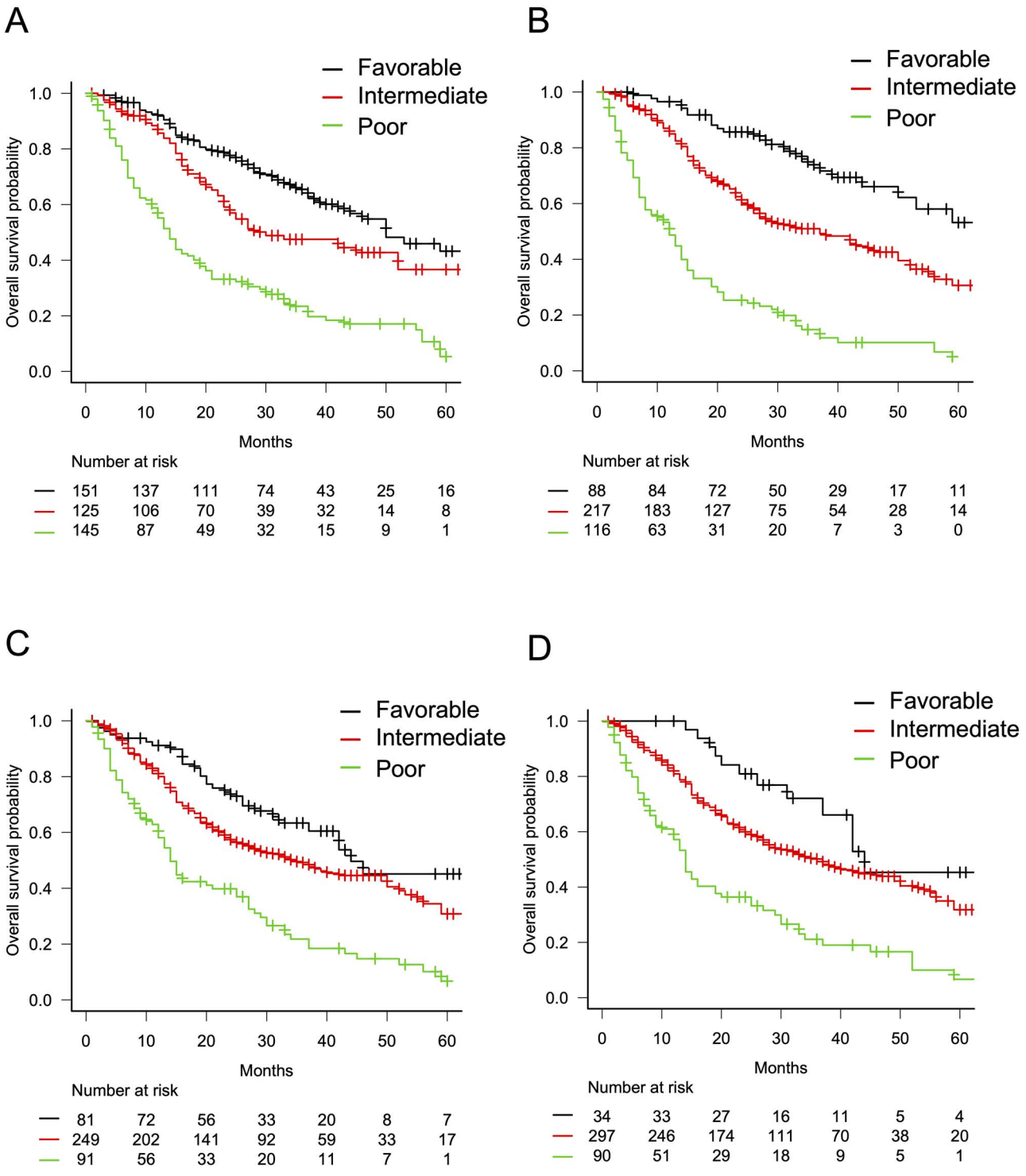

Figure 1. (A) Overall survival (OS) of 421 previously treated metastatic renal cell carcinoma (mRCC) patients according to risk classifications by the albumin, C-reactive protein and lactate dehydrogenase (ACL) model. (B) OS of the 421 previously treated mRCC patients according to risk classifications by the Japan Urologic Oncology Group (JUOG) model. (C) OS of the 421 previously treated mRCC patients according to risk classifications by the Memorial Sloan Kettering Cancer Center (MSKCC) model. (D) OS of the 421 previously treated mRCC patients according to risk classifications by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model.

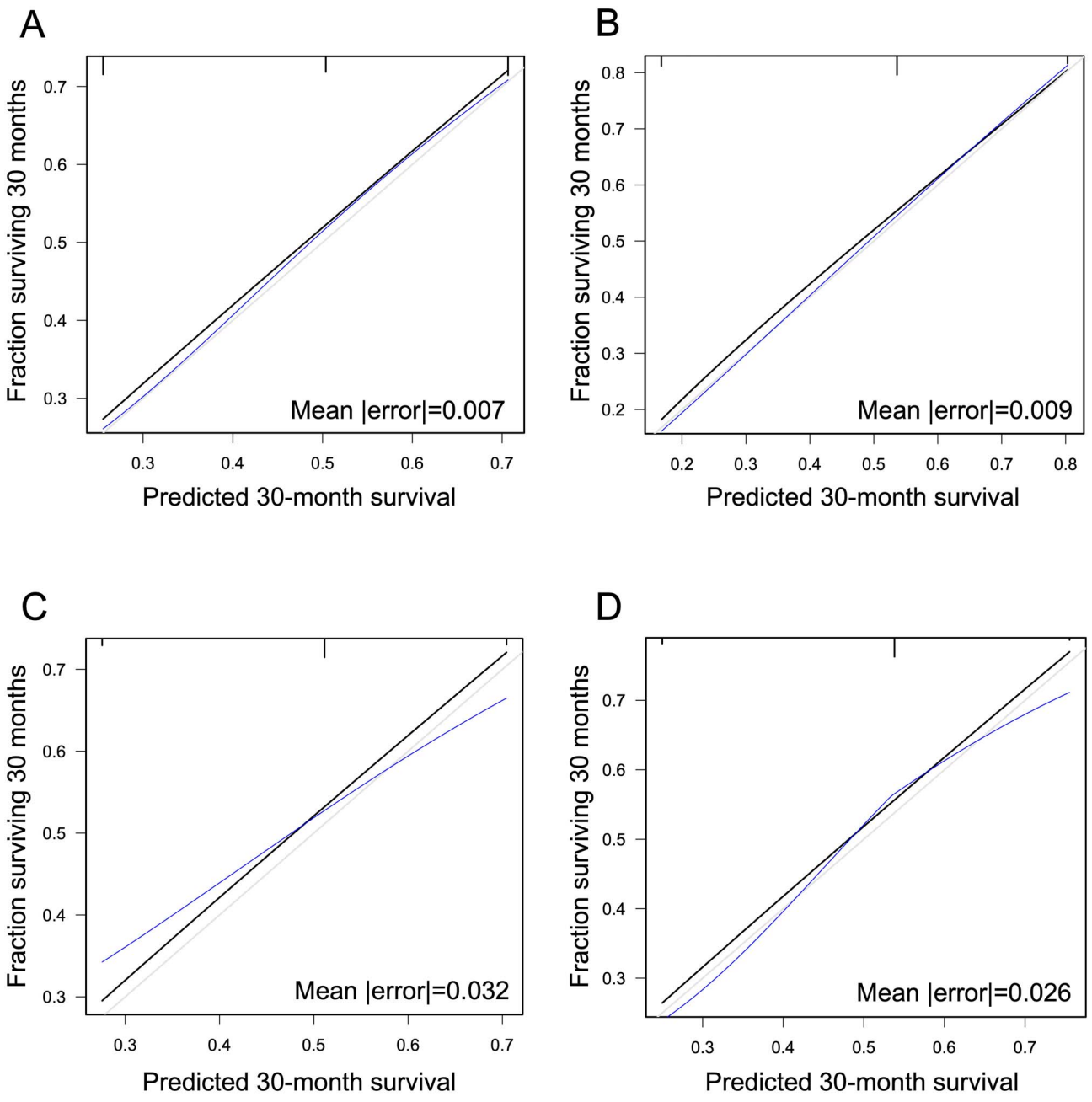

Figure 2. Calibration curves of the fraction surviving 30 months vs. predicted 30-month survival probability by ACL (A), JUOG (B), MSKCC (C) and IMDC models (D). The 5-fold cross validation is used to estimate overfitting-corrected calibration curve. Black line, observed; gray line, ideal; blue, bias corrected.

3 years after the initiation of second-line axitinib therapy than the MSKCC and IMDC models.

Discussion

Due to the recent introduction of multiple agents with different mechanisms of action into routine clinical practice, the accuracy of outcome assessments of patients with mRCC has markedly improved (1,2); however, the complexity of therapeutic strategies during sequential treatments with these effective agents for mRCC patients has markedly increased. Therefore, the role of prognostication models has become important for assessing outcomes and selecting the optimal agent for each mRCC patient. Although two conventional models, the MSKCC and IMDC models (8,9), have been regarded as standard prognostication models for previously treated mRCC patients, neither of these models were based on data obtained from mRCC patients receiving second-line targeted therapies. Based on these findings, we developed the ACL model as a useful prognostication system for OS in mRCC patients treated with second-line targeted agents (13). In the present study, using detailed data from 421 mRCC patients receiving second-line axitinib therapy at multiple institutions belonging to the JUOG, the utility of the ACL model was externally validated and its ability to predict OS in a second-line setting was compared with the newly

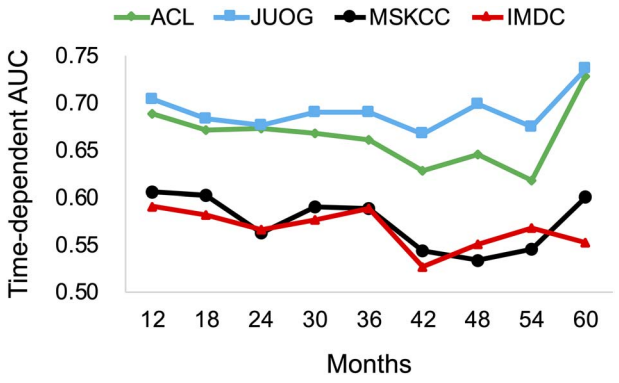

Figure 3. Comparison of changes in the time-dependent area under the receiver operating characteristic curve (AUC). AUC representing bias-corrected performance among the ACL, JUOG, MSKCC and IMDC models. AUCs were estimated using 5-fold cross validation 12, 18, 24, 30, 36, 42, 48, 54 and 60 months after the initiation of axitinib therapy.

developed JUOG model in addition to the MSKCC and IMDC models.

Median OS after the introduction of second-line axitinib in the 421 patients included in the present study was 30 months, and a multivariate analysis identified the following six factors that were independently associated with poor OS: low ECOG PS, <1 year from diagnosis to targeted therapy, an elevated neutrophil count, elevated platelet count, low Alb, elevated CRP and elevated LDH. Of these six factors, low Alb, elevated CRP and elevated LDH were incorporated into the ACL model, while the remaining three factors have also been characterized as useful prognostic parameters for mRCC patients (7,9,12, 22–24). Accordingly, the JUOG model consisting of these six independent risk factors was newly developed by dividing mRCC patients receiving second-line axitinib into favorable, intermediate and poor risk groups with no, one, or two and ≥ three risk factors, respectively. The prognosis of the 421 patients was accurately stratified by both the ACL and JUOG models; median OS in the favorable, intermediate, and poor risk groups according to the ACL model were 50, 30 and 14 months, respectively, while those according to the JUOG model was not reached, 37, and 12 months, respectively. Collectively, these results suggest that the significance of the ACL model was externally validated, and that the JUOG model is a novel and useful tool for the prognostication of previously treated mRCC patients.

It is important to evaluate the abilities of the four models (ACL, JUOG, MSKCC and IMDC models) to predict OS in mRCC patients in the second-line setting; therefore, we compared them among these four models using multiple statistical analyses, including calibration curves, C-indexes, adjusted C-indexes, time-dependent AUC and DCA, on data collected from the 421 patients. In all analyses, the ACL and JUOG models appeared to be superior for the prediction and discrimination of mRCC patients treated with second-line axitinib to the MSKCC and IMDC models. Furthermore, the C-index in the ACL model was significantly lower than that in the JUOG model; however, the remaining examinations showed similar performances between these two models. These results strongly suggest that the ACL and JUOG models are useful alternatives to the conventional prognostication system for previously treated patients with mRCC.

Despite being widely accepted, two conventional models, the MSKCC and IMDC models, are considered to have a number of limitations for their application to clinical practice. For example, IMDC models consist of six complex parameters (7,9), and non-numeric factors, which are subjectively evaluated by each physician, are contained in both models (8,9). In addition, it is generally difficult to evenly classify mRCC patients in the second-line setting into three risk groups (4,6–9). In this series, the proportion of patients corresponding to the intermediate risk stratified by these two models was also extremely high, reaching >50%. However, these features, which are regarded as critical disadvantages of these two conventional models, were also shared by the JUOG model. In contrast, the ACL model is composed of only three simple objective parameters achievable by laboratory tests, and almost equally classified the 421 mRCC patients in the present study into three risk groups. Furthermore, the ACL model was built based on data from mRCC patients treated with various types of targeted agents (13), while its utility was recognized by external validation using data from only mRCC patients receiving axitinib, commonly regraded as the most effective second-line targeted agent, in the present study (17,25,26). Therefore, even with a significantly lower C-index than the JUOG model, the ACL model is fulfilled by desired properties as a prognostication model system for previously treated mRCC patients.

There were several limitations to this study. Although a large sample size was examined, this was a multicenter retrospective study, and the study period was long. Thus, systemic therapy for the patients included was not conducted under a unified principal, and therapeutic strategies for the sequential treatment of mRCC patients themselves have changed with the introduction of novel agents during the study period. Furthermore, due to the lack of data on KPS in this series, data assessments were performed by assuming ECOG PS ≥ 2 as KPS < 80%, which may subtly affect the results obtained in the present study.

Moreover, although TKIs, including axitinib, may play an important role in a second-line setting after the introduction of immune checkpoint inhibitor-based combination therapies as a first-line treatment (27, 28), it remains unclear whether the ACL model has the ability to precisely stratify the prognosis of mRCC patients, irrespective of first-line therapeutic regimens. Therefore, further studies are needed to confirm whether the ACL model is a useful prognostication system for mRCC patients receiving first-line immune checkpoint inhibitor-based combination therapies.

Conclusions

In the present study, using data obtained from 421 mRCC patients receiving second-line axitinib therapy, we externally validated the significance of the ACL model and confirmed its usefulness for assessing the outcomes of mRCC patients in a second-line setting. Furthermore, a novel JUOG model was built based on the data collected from these 421 patients, and the prognostication performances of the four models, including the ACL, JUOG, MSKCC and IMDC models, were compared by multiple statistical analyses. Based on a comprehensive consideration of the results obtained in addition to the proportion of patients classified into three risk groups by each model, we concluded that the ACL model, consisting of three simple and objective parameters, appears to be the most suitable prognostication system for previously treated mRCC patients.

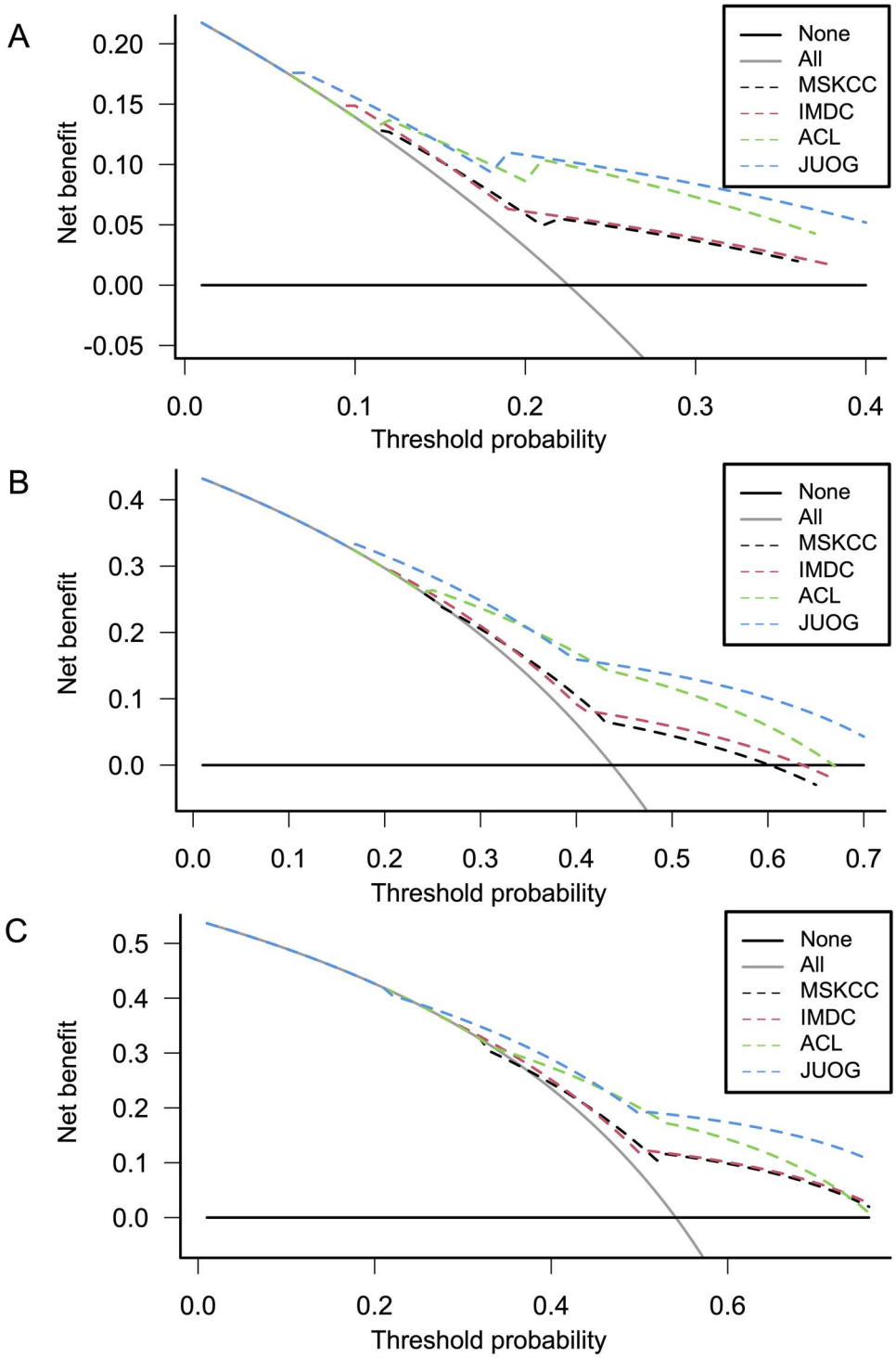

Figure 4. Comparison of decision curve analyses 1 (A), 2 (B) and 3 years (C) after the initiation of axitinib for second-line targeted therapy in 421 previously treated metastatic renal cell carcinoma patients among ACL, JUOG, MSKCC and IMDC models. None, the net benefit of treating no patients assuming that all would be alive; all, the net benefit of treating all patients regardless of their severity assuming that all would die.

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References

1. Bedke J, Gauler T, Grunwald V, et al. Systemic therapy in metastatic renal cell carcinoma. *World J Urol* 2017;35:179–88.
2. Flippot R, Escudier B, Albiges L. Immune checkpoint inhibitors: toward new paradigms in renal cell carcinoma. *Drugs* 2018;78:1443–57.
3. Calvo E, Ravaud A, Bellmunt J. What is the optimal therapy for patients with metastatic renal cell carcinoma who progress on an initial VEGFr-TKI? *Cancer Treat Rev* 2013;39:366–74.
4. Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. *World J Urol* 2018;36:1943–52.
5. Miyake H, Miyazaki A, Imai S, Harada K, Fujisawa M. Early tumor shrinkage under treatment with first-line tyrosine kinase inhibitors as a predictor of overall survival in patients with metastatic renal cell carcinoma: a retrospective multi-institutional study in Japan. *Target Oncol* 2016;11:175–82.
6. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;20:289–96.
7. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009;27:5794–9.
8. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;22:454–63. doi: 10.1200/JCO.2004.06.132.
9. Ko JJ, Xie W, Kroeger N, et al. The international metastatic renal cell carcinoma database consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. *Lancet Oncol* 2015;16:293–300.
10. Eggers H, Ivanyi P, Hornig M, Grunwald V. Predictive factors for second-line therapy in metastatic renal cell carcinoma: a retrospective analysis. *J Kidney Cancer VHL* 2017;4:8–15.
11. Levy A, Menard J, Albiges L, et al. Second line treatment of metastatic renal cell carcinoma: the Institut Gustave Roussy experience with targeted therapies in 251 consecutive patients. *Eur J Cancer* 2013;49:1898–904.
12. Chrom P, Kawecki M, Stec R, Bodnar L, Szczylik C, Czarnecka AM. Biomarkers defining probability of receiving second-line targeted therapy in metastatic renal cell carcinoma. *Med Oncol* 2018;35:91.
13. Tamura K, Matsushita Y, Watanabe H, et al. Feasibility of the ACL (albumin, C-reactive protein and lactate dehydrogenase) model as a novel prognostic tool in patients with metastatic renal cell carcinoma previously receiving first-line targeted therapy. *Urol Oncol* 2020;38:6.e9–6.e16.
14. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–34.
15. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–24.
16. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369:722–31.
17. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;378:1931–9.
18. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a frame-work for traditional and novel measures. *Epidemiology* 2010;21:128–38.
19. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87.
20. Subramanian J, Simon R. An evaluation of resampling methods for assessment of survival risk prediction in high-dimensional settings. *Stat Med* 2011;30:642–53.
21. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006;26:565–74.
22. Guo S, He X, Chen Q, et al. The C-reactive protein/albumin ratio, a validated prognostic score, predicts outcome of surgical renal cell carcinoma patients. *BMC Cancer* 2017;17:171.
23. Hu Q, Gou Y, Sun C, et al. The prognostic value of C-reactive protein in renal cell carcinoma: a systematic review and meta-analysis. *Urol Oncol* 2014;32:e1-8.
24. Beuselinck B, Vano YA, Oudard S, et al. Prognostic impact of baseline serum C-reactive protein in patients with metastatic renal cell carcinoma (RCC) treated with sunitinib. *BJU Int* 2014;114:81–9.
25. Bracarda S, Bamias A, Casper J, et al. Is Axitinib still a valid option for mRCC in the second-line setting? Prognostic factor analyses from the AXIS trial. *Clin Genitourin Cancer* 2019;17:e689–703.
26. Schmidinger M, Porta C, Oudard S, et al. Real-world experience with Sunitinib treatment in patients with metastatic renal cell carcinoma: clinical outcome according to risk score. *Clin Genitourin Cancer* 2020;6: S1558-7673(20)30047-1.
27. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1116–27.
28. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1103–15.