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Prognostic factors for overall survival in patients with clear cell metastatic renal cell carcinoma

Model development and external validation with Memorial Sloan Kettering Cancer Center model and the international metastatic renal cell carcinoma database consortium model

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Abstract

To develop a new prognostic model for the overall survival of patients with clear cell metastatic renal cell carcinoma (mRCC) using Korean Renal Cancer Study Group (KRoCS) database and compared it with 2 renowned prognostic models: the Memorial Sloan Kettering Cancer Center (MSKCC) and the international metastatic renal cell carcinoma database consortium (IMDC) models.

Data of 790 patients diagnosed with mRCC and receiving targeted therapy as their first-line treatment were pooled to this study. Data from 4 hospitals (n = 619) were used to develop the new model and those from other 5 hospitals (n = 171) were used for external validation. After detecting prognostic factors in multivariable Cox proportional-hazards regression analysis, patients were classified into 3 risk groups, favorable (0), intermediate (1–2), and poor (3 and more) by the number of prognostic factors.

Seven variables such as more than 2 metastasis sites, no prior nephrectomy, Eastern Cooperative Oncology Group performance status ≥2, low hemoglobin, high serum corrected calcium, high neutrophil, high serum alkaline phosphatase were identified as prognostic factors for poor overall survival. Also, risk groups were categorized into 3 groups; median overall survival was 61.1 months in favorable, 26.5 months in intermediate, and 6.8 months in poor group. KRoCS ranked the first in all 3 statistical parameters including akaike information criterion (AIC), concordance index and generalized R^2 among other prognostic models.

We developed the KRoCS model and validated it externally with demonstrating its superiority over MSKCC and IMDC models. The KRoCS model can provide useful information for counseling patients with clear cell mRCC regarding life-expectancy.

Abbreviations: AIC = akaike information criterion, cCa = corrected calcium, ECOG = European Cooperative Oncology Group, EV = external validation, Hb = hemoglobin, IMDC = international metastatic renal cell carcinoma database consortium, KRoCS = Korean Renal Cancer Study Group, MD = model-developing, mRCC = metastatic renal cell carcinoma, MSKCC = Memorial Sloan Kettering Cancer Center, OS = overall survival.

Keywords: biomarkers, kidney neoplasms, prognostic factors, renal cell carcinoma, survival rate

Editor: Suman Suman.

The authors have no conflicts of interests to disclose.

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Shin D, Jeong CW, Song C, Kang M, Seo SI, Kim JK, Lee H, Chung J, Hong SH, Hwang EC, Kwak C, Park JY. Prognostic factors for overall survival in patients with clear cell metastatic renal cell carcinoma: Model development and external validation with Memorial Sloan Kettering Cancer Center model and the international metastatic renal cell carcinoma database consortium model. Medicine 2021;100:31(e26826).

Received: 11 January 2021 / Received in final form: 3 May 2021 / Accepted: 19 July 2021

http://dx.doi.org/10.1097/MD.0000000000026826

1. Introduction

The paradigm of treating metastatic renal cell carcinoma (mRCC) has changed in decades from immunotherapy, targeted therapy to immuno-oncology combination treatment.[1,2] In the immunotherapy era, Memorial Sloan Kettering Cancer Center (MSKCC) model was the first model to propose risk factors for the survival of patients with mRCC.[3] MSKCC analyzed mRCC patients involved in clinical trials conducted between 1975 and 1996.[3] On the other hand, the international metastatic renal cell carcinoma database consortium (IMDC) model is one of the standard models in the targeted therapy era.[4] IMDC study was based on patients who underwent targeted therapy as their first-line treatment between 2004 and 2008.[4] In addition, IMDC model was compared with 4 other previous models including the MSKCC model.[5,6] At present, the treatment choice for patients with mRCC starts from risk stratification of each patient.[2]

There are several globally renowned prognostic models regarding the survival of patients with mRCC.[3,4,7–13] However, there has been no study conducting in clear cell mRCC exclusively. Previous studies were mostly based on Western population[3,4,7–13] and treatment strategies also vary between immunotherapy and targeted therapy. Notably, a few Japanese studies were performed in Asian patients,[12,13] however these patients received immunotherapy as the first-line therapy which was a trend in the past and there has been no study performed in Asian patients receiving targeted therapy. Furthermore, since clear cell consists 83% to 88% of the RCC pathologic type and other types of RCC have different prognosis,[14] it is worthwhile to study strictly on clear cell mRCC. When a new model is designed, it should be tested against previous renowned models to substantiate its performance. The aim of this study is to develop a new prognostic model with data solely comprised of clear cell mRCC and compare its performance with MSKCC and IMDC.

2. Materials and methods

2.1. Patient population

We used Korean Renal Cancer Study Group (KRoCS) database, which contains data of patients with clear cell mRCC collected in 9 hospitals in Korea:[15] Samsung Medical Center, Asan Medical Center, Seoul National University Bundang Hospital, Seoul National University Hospital, National Cancer Center, Seoul St Mary's Hospital, Chonnam National University Hwasun Hospital, Wonkwang University Hospital, Korea University Medical Center. In the model-developing (MD) cohort, we pooled 619 patients from 4 hospitals (Samsung Medical Center, Seoul National University Bundang Hospital, National Cancer Center, Chonnam National University Hwasun Hospital) who were diagnosed with mRCC from July of 2000 to July of 2017. Also, we selected 171 patients from the other 5 hospitals who were diagnosed with mRCC within the same period aforementioned and designated the patients as external validation (EV) cohort. All patients in both cohorts received a single targeted therapy agent including tyrosine kinase inhibitor or mammalian target of rapamycin inhibitor as their first-line treatment. Patients who received immunotherapy as their first-line treatment were excluded. Institutional Review Boards at all participating institutions approved this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a prior approval by the Institutional Review Board of Korea University Ansan Hospital (approval number: 2015AS0530). Due to retrospective enrollment, written informed consent from patients was waived.

2.2. Baseline characteristics

Baseline characteristics of participants to be investigated were age at targeted therapy initiation, sex, European Cooperative Oncology Group (ECOG) performance status, metastasis type, number of metastasis sites, prior nephrectomy, first line treatment, time from diagnosis to start of treatment, diabetes mellitus, hypertension, and laboratory findings such as serum hemoglobin (Hb), corrected calcium (cCa), alkaline phosphatase, lactate dehydrogenase, platelet, and neutrophil level. Following prior studies such as IMDC[4] and MSKCC,[3] serum cCa was used instead of total serum calcium and cCa was calculated as followed: $cCa = Ca - 0.7 \times (\text{serum albumin} - 3.4)$. All the aforementioned variables were categorized with the same cut-value as previous studies had adopted.[3,4,12] Low Hb means $Hb < 13.5$ g/dL for male and $Hb < 11.5$ g/dL for female patients; high cCa means cCa >10.0 mg/dL; high neutrophil means neutrophil $>7000/\mu L$; high platelet means platelet $>400{,}000/\mu L$; high ALP means ALP >88 U/L for patients under age of 55 and ALP >115 U/L for patients above age of 55; high LDH equals LDH ≥ 300 U/L.

2.3. Statistical analysis

Our primary endpoint was finding clinically significant factors for the clear cell mRCC survival and developing KRoCS model predicting clear cell mRCC prognosis. Using the MD cohort, we implemented univariable analysis to determine potentially significant variables among baseline characteristics. Successively, we proceeded to multivariable analysis using Cox proportional hazards model to discover prognostic factors for KRoCS. In the statistical analysis procedure, stepwise backward method was used with variables entering with P value of .15 and remaining at .05.[3,4] Furthermore, we scrutinized Cox model's proportional hazard assumption with plots of log - log[survival] versus log of survival time, and variables not meeting the assumption were excluded before entering Cox proportional hazards analysis. Next, we categorized patients in 3 risk groups by the same number of prognostic factors as previous models such as MSKCC and IMDC. After categorization, we graphically displayed the overall survival (OS) of patients with Kaplan-Meier method and compared OS of each groups by the log-rank test. OS was defined as time from treatment initiation to death or last follow-up date.

Subsequently, we executed external validation which compares the performance of KRoCS with those of existing models such as MSKCC and IMDC using the EV cohort. We performed Cox proportional hazards regression in all 3 models and calculated statistical parameters such as akaike information criterion (AIC),[16] concordance index,[17] and generalized R^2[18] to assess model fit. AIC is a relative estimator of model fit or the discriminating ability in a given sample, and its low value implies a good fit. C-index is an area under receiver operating curve at which 0.5 implies random discrimination and 1 represents perfect discrimination. Generalized R^2 is coefficient of determination that high value represents a good fit. Altogether, low AIC, high concordance index, and high generalized R^2 suggests a good model fit. Moreover, as 3 models classify 3 risk groups, we assessed the ratio of the number of patients allocated in each risk groups by Chi-Squared test. Firstly, the ratio of patients

categorized by KRoCS model in MD cohort was compared with ratio of patients categorized by KRoCS model in EV cohort. Successively, the ratio of patients categorized by KRoCS model in MD cohort was compared with those of MSKCC and IMDC in EV cohort. Lastly, we performed Kaplan–Meier analysis and log-rank test to visualize categorized risk groups and assess the validity of categorization in each model. In all analysis, missing values in explanatory variables were managed with case-deletion method, and loss to follow-up was also eliminated from the analysis. Statistical analysis was performed with R (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

3. Result

3.1. Patient characteristics and univariable analysis

Table 1 presents baseline characteristics of cohorts that were used in model development (n = 619) and external validation (n = 171). Both cohorts had complete data without any missing values. The median OS was 21.6 months (IQR, 8.2–61.0 months) and the median follow up time was 36.0 months (IQR, 20.1–62.9 months) in MD cohort. In this group, the mean age at the diagnosis of metastasis was 59 years (95% CI, 58–60 years) and the mean age at receiving first line treatment was 60 years (95% CI, 58–61 years). The median time from diagnosis to start of treatment was 1.4 months (IQR, 0.6–3.2 months). The median OS was 30.8 months (IQR, 9.3–64.0 months) and the median follow up time was 61.0 months (IQR, 28.4–86.7 months) in EV cohort. The mean age at the diagnosis of metastasis, the mean age at receiving first line treatment, and the median time from diagnosis to start of treatment) in EV cohort were 58 years (95% CI, 58–60 years), 58 years (95% CI, 58–60 years), and 1.2 (IQR, 0.6–3.1), respectively. Table 1 also demonstrates the result of univariable analysis for overall survival on the potential variables for KRoCS model. Among the variables, metastasis type, number of metastasis sites, ECOG performance status, prior nephrectomy, low hemoglobin (male < 13 g/dL, female <11.5 g/dL), high serum corrected calcium (>10.0 mg/dL), high neutrophil (>7000/μL), high serum alkaline phosphatase (age under 55 >88 U/L, age above 55 >115 U/L) had relationship with OS with P value under .05.

3.2. Multivariable analysis and risk group assessment

The result of multivariable Cox proportional hazard model is shown in Table 2. Metastasis type was not included in the multivariable analysis, for it was suspected to have collinearity with prior nephrectomy. In addition, age at first line treatment and sex did not meet Cox proportional hazards assumption and thus were removed in multivariable analysis. Consequently, 7 variables were identified as prognostic factors of OS and incorporated into KRoCS model: No prior nephrectomy ($P <$ .001), ECOG above 2 ($P = .014$), low hemoglobin ($P < .001$), high serum corrected calcium ($P = .005$), high neutrophil ($P < .001$), high serum alkaline phosphatase ($P < .001$), and more than 2 metastasis sites ($P < .001$). The patients were stratified into 3 risk groups by the same number of risk factors as presented by MSKCC and IMDC: favorable (0), intermediate (1–2), poor (3 and more). As the results depicted in Figure 1, favorable group had 102 patients with median OS of 61.1 months (95% CI 41.5–not reached), while intermediate had 362 patients with median OS of 26.5 months (95% CI 22.7–31.3), and poor group had 155 patients and median OS of 6.72 months (95% CI 5.0–8.9). Taken together, KRoCS showed clear distinctions between risk groups (log rank $P < .001$).

3.3. External validation

As presented in Table 3, 171 patients in the EV cohort were separated in 3 risk groups as each model (KRoCS, MSKCC, and IMDC) suggested. In favorable risk group, MSKCC designated the largest number of patients (n = 58, 34%), while IMDC had the largest number of patients (n = 141, 82%) in intermediate risk group. It is also noteworthy that IMDC classified the majority of patients as intermediate risk (82%), which deviated from other models. In poor risk group, KRoCS (n = 50, 29%) separated the largest number of patients. Figure 2 delineates how each model stratifies patients by risk groups. All 3 models distinguished patients significantly with P value less than .001 in log-rank test. MSKCC and IMDC models were only moderately concordant with KRoCS, with 64% and 55% of patients categorized into the same risk group, respectively. The distribution of favorable/intermediate/poor risk group in model-developing cohort by KRoCS was 17/58/25% respectively, which was the most similar distribution in external validation cohort by KRoCS (17/54/29% respectively) among other models. Additionally, we performed Chi-Squared test, which compared the ratio of patients allocated in each risk groups, to advocate the consistency of KRoCS model in another population. Compared to the distribution of favorable/intermediate/poor risk group in model-developing cohort by KRoCS (n = 619) that serves as the reference, the distribution of favorable/intermediate/poor risk group in external validation cohort by KRoCS (n = 171) was not significantly different in Chi-Squared test (P value = .48). On the other hand, distributions by MSKCC and IMDC was significantly different compared to the reference (P value < .05).

Table 2 illustrates the result of multivariable Cox proportional hazards analysis of KRoCS in the model-developing cohort (n = 619) and the external validation cohort (n = 171). The hazard ratio calculated using the validation cohort was comparable to that from original model, which implies exemplary external validation. The concordances in both cohorts were similar, which resulted 0.71 (95% CI 0.68–0.73) in the MD cohort and 0.69 (95% CI 0.64–0.74) in the EV cohort. This further advocates the excellence of external validation. Ultimately, we employed Cox proportional hazards model in each validation groups to calculate statistical parameters to compare model fit (Table 4). In all 3 parameters, KRoCS ranked the first, and MSKCC and IMDC followed in order indicating that KRoCS model has the best model fit among others.

4. Discussion

KRoCS model is the first one to propose prognosticators for overall survival of patients with clear cell mRCC in Korea. Our model found 7 variables which distinguishes itself from previous models such as MSKCC and IMDC: ECOG performance status ≥2, no prior nephrectomy, number of metastasis sites ≥2, low hemoglobin, high neutrophil, high serum corrected calcium, and high serum alkaline phosphatase. The model was validated externally with data from other 5 hospitals which were not involved in the model developing process. Furthermore, KRoCS model was compared with MSKCC and IMDC models using log-

Table 1

Baseline characteristics of patients with clear cell metastatic renal cell carcinoma from Korean Renal Cancer Study Group (KRoCS) database and univariable analysis for overall survival.

	Model cohort (N = 619 cases)		External validation cohort (N = 171 cases)		
Variable	**Mean (SD)**	**No (%)**	**Mean (SD)**	**No (%)**	**Univariable Analysis (*P* value)**
Age at mRCC diagnosis (yr)	59.2 (11.4)		58.0 (11.5)		
Age at first line treatment (years)	59.5 (11.4)		58.4 (11.6)		.529
Age ≥60		311 (50.2)		87 (50.9)	
Age <60		308 (49.8)		84 (49.1)	
Overall survival					
Median		21.6		30.8	
Interquartile range		19.1–26.6		22.1–40.6	
Gender					.292
Male		485 (78.4)		134 (78.4)	
Female		134 (21.6)		37 (21.6)	
Metastasis					<.001
Synchronous		389 (62.8)		103 (60.2)	
Metachronous		230 (37.2)		68 (39.8)	
Site of metastatic disease					
Lung		441 (71.2)		127 (74)	
Lymph node		233 (37.6)		79 (46.2)	
Bone		185 (29.9)		50 (29.2)	
Liver		81 (13.1)		32 (18.7)	
Brain		50 (8.0)		14 (8.2)	
Others		148 (23.9)		46 (26.9)	
Number of metastasis sites					<.001
<2		277 (44.7)		61 (36.0)	
≥2		342 (55.3)		110 (64.0)	
ECOG performance status					<.001
<2		588 (95.0)		151 (88.3)	
≥2		31 (5.0)		20 (11.7)	
Prior Nephrectomy					<.001
Yes		524 (84.7)		136 (79.5)	
No		95 (15.3)		35 (20.5)	
Treatment					
Sunitinib		315 (50.9)		104 (60.8)	
Sorafenib		65 (10.5)		15 (8.8)	
Pazopanib		195 (31.5)		29 (17.0)	
Axitinib		0 (0)		1 (0.6)	
Bevacizumab		9 (1.5)		1 (0.6)	
Everolimus		15 (0.6)		2 (1.2)	
Temsirolimus		31 (5.0)		19 (11.1)	
Hb (g/L) < LLN	12.7 (2.3)	300 (48.5)	13.0 (2.0)	69 (40.4)	<.001
ALP (U/L) > ULN	118.5 (104.2)	217 (35.0)	114.2 (100.5)	55 (32.0)	<.001
Platelet ($\times 10^3/\mu L$) > ULN	227.0 (110.0)	43 (7.0)	196.2 (93.3)	3 (1.8)	<.001
Neutrophil ($/\mu L$) > ULN	4092.5 (3084.6)	58 (9.4)	3775 (1865.9)	8 (4.7)	<.001
LDH (U/L) > ULN	322.3 (222.5)	113 (18.3)	288.9 (164.7)	51 (29.8)	.294
Albumin (g/dL)	4.0 (0.6)		3.8 (0.5)		<.001
Corrected Ca (mg/dL) > ULN	9.1 (0.7)	38 (6.1)	9.0 (0.6)	9 (5.3)	<.001

ALP = alkaline phosphatase, ECOG = Eastern Cooperative Oncology Group, Hb = hemoglobin, LDH = lactate dehydrogenase, LLN = lower limit of normal, mRCC = metastatic renal cell carcinoma, ULN = upper limit of normal.

rank test, Chi-Squared test and Cox proportional hazards analysis.

Although patients in IMDC had about the same median OS (22 months) compared to those in KRoCS,[4] IMDC model appeared to overestimate the median survival of the favorable group compared to other 2 models as it allocated only a small number (n = 7) of patients to not reach median OS. In addition, it tended to inordinately categorize more patients in intermediate group than the other 2 models (n = 141, Table 3), and its model fit appeared to lag behind by KRoCS and MSKCC, albeit in a narrow margin (Table 4). Overall, this was an interesting phenomenon because IMDC model is the most commonly used model nowadays, and, correspondingly, all patients in KRoCS had also received targeted therapy as their first-line treatment according to the stratification from this model. On the other hand, MSKCC model, which was established in the immunotherapy era, was not inferior to IMDC model in this study. In fact, MSKCC has been still widely adopted in the major guidelines until nowadays and was still a potent model when tested in our population. This may be due to the importance of variable "prior nephrectomy," which was also highlighted in other previous studies,[12,19,20] and the fact that 4 out of 5 variables in MSKCC were the same as that of KRoCS. In the extended study of MSKCC model tested in targeted therapy era,[20] 5 prognostic factors including "LDH" and "more than 2 metastasis sites" were identified. The latter was an update from the original

Table 2

Result of multivariable Cox proportional-hazard regression analysis in model developing cohort and external validation cohort.

	Model developing cohort (n = 619)		External validation cohort (n = 171)	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
No prior nephrectomy	1.9 (1.5–2.5)	<.01	2.2 (1.4–3.5)	<.01
ECOG performance status ≥2	1.7 (1.1–2.6)	.01	1.1 (0.6–1.9)	.82
Metastasis sites ≥2	1.8 (1.5–2.3)	<.01	1.9 (1.2–3.1)	<.01
Low hemoglobin	1.7 (1.4–2.2)	<.01	1.5 (1.0–2.2)	.06
High serum corrected calcium	1.8 (1.2–2.8)	<.01	1.4 (0.6–3.2)	.48
High serum alkaline phosphatase	1.6 (1.3–2.0)	<.01	1.8 (1.2–2.8)	<.01
High neutrophil	1.8 (1.3–2.4)	<.01	1.7 (0.7–4.0)	.25

CI = confidence interval, ECOG = European Cooperative Oncology Group.

MSKCC model and may support the importance of metastasis in forecasting poor prognosis as largely approved by previous studies.[8,11] Notably, IMDC did not sufficiently investigate metastasis sites as it lacked patient information in bone metastasis,[4,20] which was stated as one of the most common sites of disease progression in mRCC patients by Plimack et al.[21] MSKCC model seems generally applicable, however, one of its variables LDH is not a routine laboratory variable collected in our country, which imposes inconvenience for physicians to make prognostic decisions. LDH was not included in our analysis because only 18% of total patients (n = 3095) had LDH value in KRoCS database that includes 9 major hospitals in Korea. Taken together, KRoCS model can be a practical model that not only acknowledges the trends of variable selection in previous studies, but also consists of variables that are readily measurable in most facilities in this country.

In our analysis, IMDC and KRoCS model showed difference in terms of distribution of risk groups. KRoCS model in MD cohort

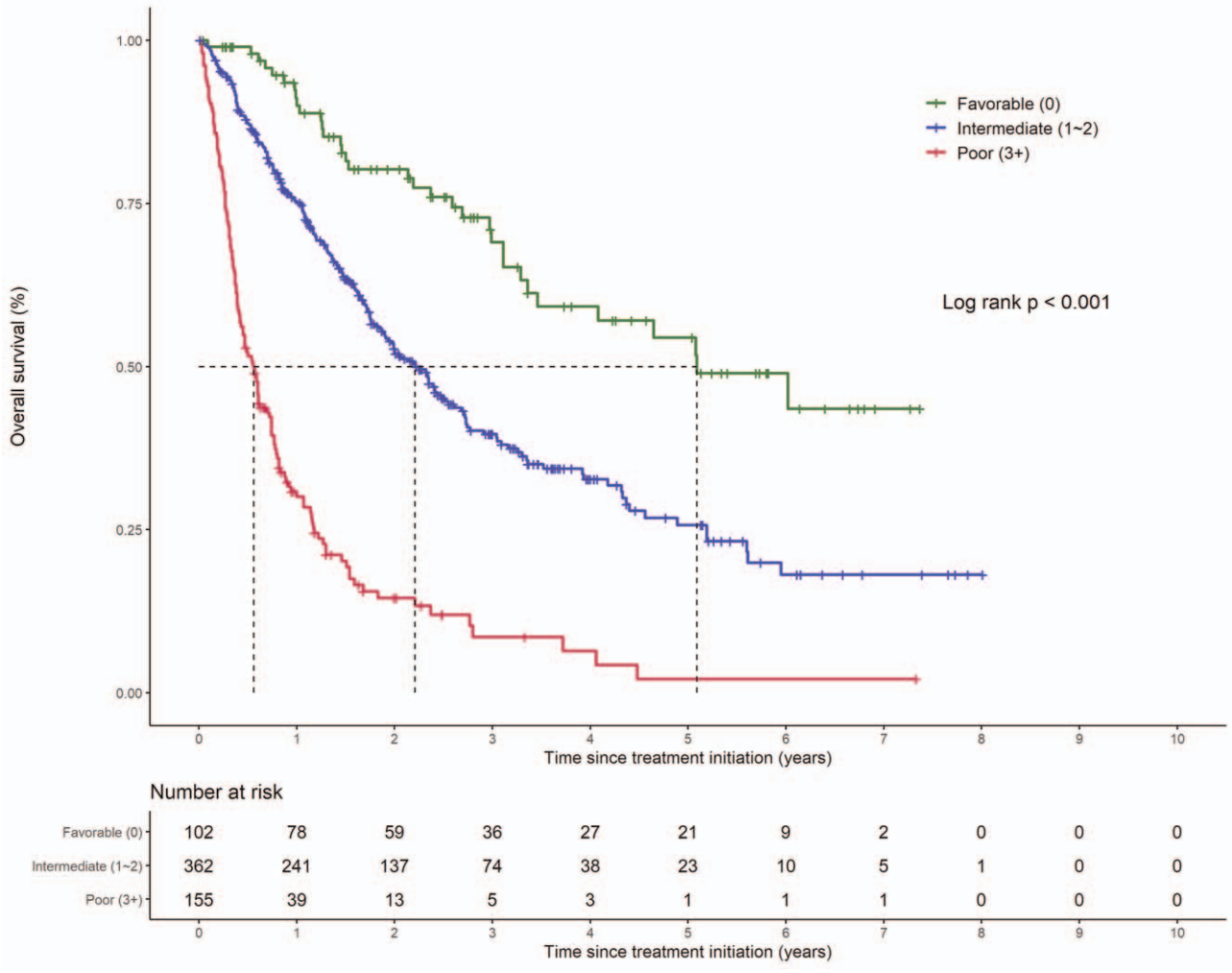

Figure 1. Kapan–Meier curve of stratified risk groups by KRoCS model in model developing cohort.

Table 3

Selected risk factors and median overall survival in metastatic renal cell carcinoma survival predicting models.

	Model		KRoCS		MSKCC[3]		IMDC[4]	
Patient cohort	**Model-developing (n = 619)**		**External validation (n = 171)**		**External validation (n = 171)**		**External validation (n = 171)**	
ECOG performance status	○	○	○	○				
Low hemoglobin	○	○	○	○				
High serum corrected calcium	○	○	○	○				
High neutrophil	○	○		○				
High serum platelet				○				
High serum alkaline phosphatase	○	○						
High serum lactate dehydrogenase			○					
No prior nephrectomy	○	○	○					
Time from diagnosis to treatment <1 year				○				
Metastasis sites ≥2	○	○						
Risk groups	Number	Median OS (months) (IQR)	Number	Median OS (months) (IQR)	Number	Median OS (months) (IQR)	Number	Median OS (months) (IQR)
Favorable (0 risk factors)	102 (17%)	61.1 (31.1–NA)	29 (17%)	51.6 (20.6–NA)	58 (34%)	47.1 (20.6–NA)	7 (4%)	NA
Intermediate (1–2 risk factors)	362 (58%)	26.5 (12.7–62.2)	90 (53%)	35.6 (12.7–64.0)	94 (56%)	30.8 (8.9–51.6)	141 (82%)	33.8 (11.4–64.0)
Poor (≥3 risk factors)	155 (25%)	6.7 (3.3–14.2)	52 (30%)	9.3 (6.2–40.6)	19 (10%)	7.4 (3.9–15.2)	23 (14%)	7.2 (3.9–12.5)

KRoCS = Korean Renal Cancer Study Group, IMDC = international metastatic renal cell carcinoma database consortium, MSKCC = Memorial Sloan Kettering Cancer Center, ECOG = Eastern Cooperative Oncology Group, OS = overall survival, IQR = interquartile range, NA = not reached.

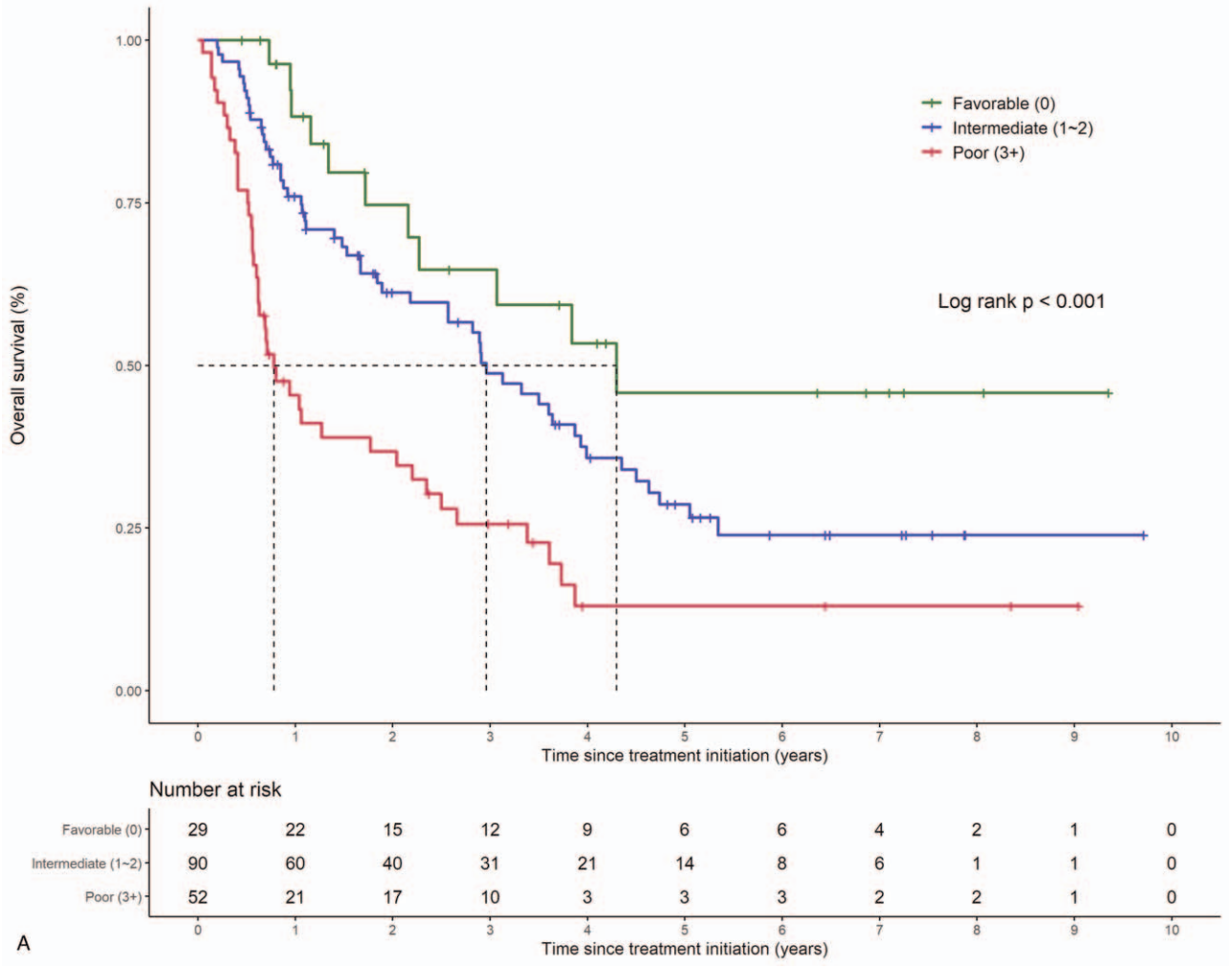

Figure 2. Kaplan–Meier curve of stratified risk groups by metastatic renal cell carcinoma prognostic models in external validation cohort (A. KRoCS model, B. MSKCC model, C. IMDC model).

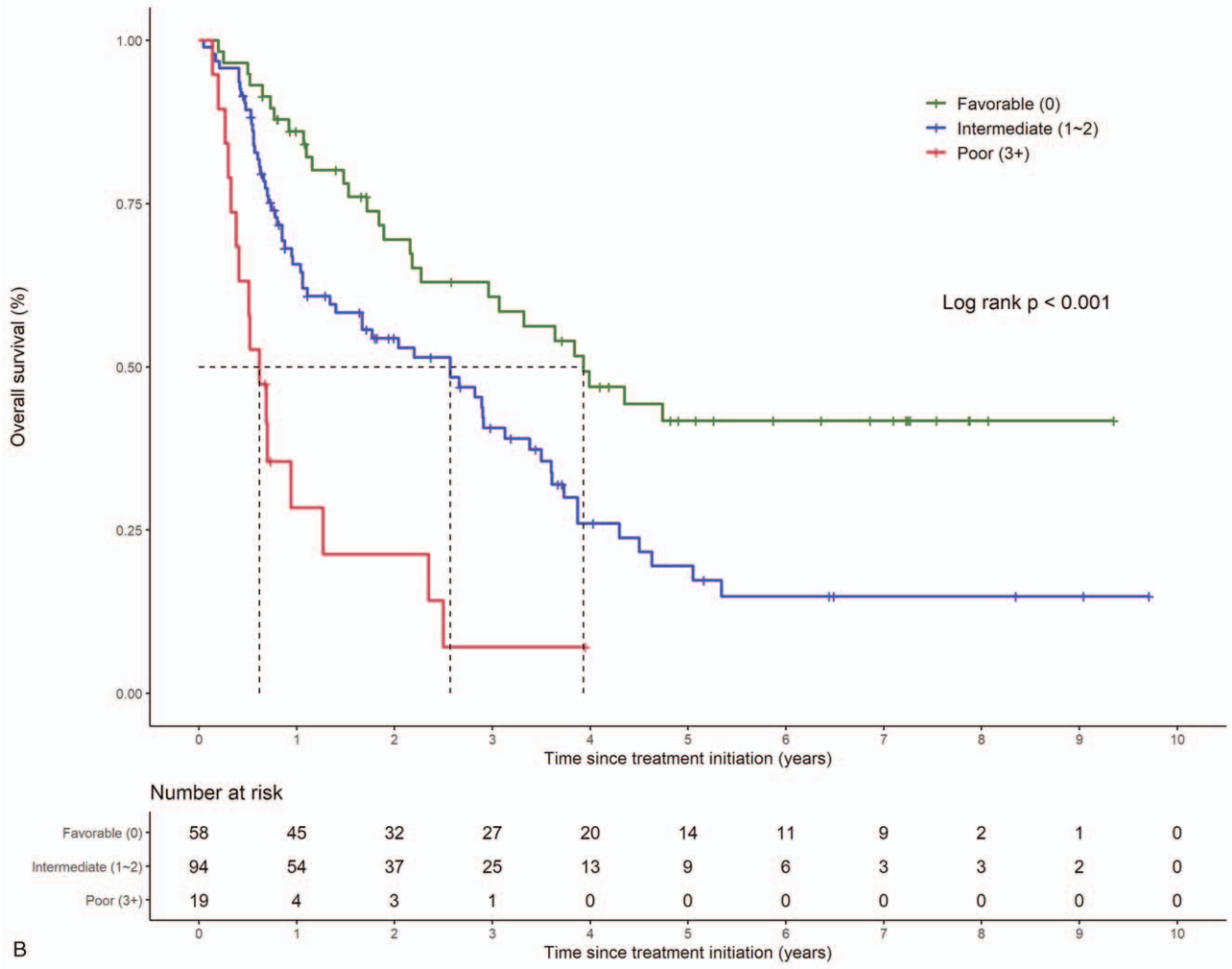

Figure 2. (Continued)

have 17% of patients in the favorable risk group and 58% of patients in the intermediate risk group, whereas 4% of patients in the favorable risk group and 82% of patients are in the intermediate risk group in IMDC model. Previous study comparing treatment efficacy of Asian with that of non-Asian patients[22–24] demonstrated that Western and Asian patients with mRCC administered with targeted therapies did not have disparities in OS. However, many literatures ascertain increased toxicity of sunitinib such as hand-foot-syndrome, thrombocytopenia, stomatitis, and fatigue in Asian patients.[23–27] Genetic predispositions as well as low body surface area may explain such vulnerabilities.[26–29] Despite the efficacy of sunitinib was appeared to be similar in both ethnicities,[22–25,29] higher rate of dose reduction and discontinuation of drug in Asian patients may have resulted in inadequate response.[23,25–27,30] However, in the current study, median OS in favorable and intermediate risk group were far longer than those of the previous studies performed in Western countries. In EV cohort, median OS were 52 months and 36 months in favorable and intermediate risk group, respectively, whereas median OS in favorable risk group was 27 to 42 months and median OS in intermediate risk group was 12 to 29 months in the previous studies.[7,8,11] These excellent results may come from better management for side effects due to the pooled experiences in treating the patients with mRCC. Taken together, this new KRoCS model could discriminate the risk of mRCC patients better than MSKCC and IMDC models in our dataset. There are also several limitations in this study. Firstly, we substituted ECOG performance score for Karnofsky performance score (KPS) which was used as one of the variables in the previous studies. However, ECOG performance score demonstrated more ability than KPS to discriminate patients with different prognosis as suggested by Buccheri et al.[31] In addition, ECOG performance score was shown to have interchange ability with KPS.[32] Secondly, since this study is based on retrospective cohort, it is innately susceptible to selection bias. Lastly, in our dataset, variable LDH which is one of the prognosticators in MSKCC model was largely missing (66%). Therefore, the significance of this variable may have been influenced by the reduced number of total patients examined in the univariable analysis than that of other variables. However, LDH, which was not a routine laboratory test for mRCC patients, is now one of the variables collected in KRoCS database. Therefore, its clinical meaning could be discovered in our next analysis.

In conclusion, we identified 7 prognostic factors for the poor prognosis of patients with clear cell mRCC in the targeted therapy era and categorized patients into 3 groups by the number of prognostic factors. External validation including statistical

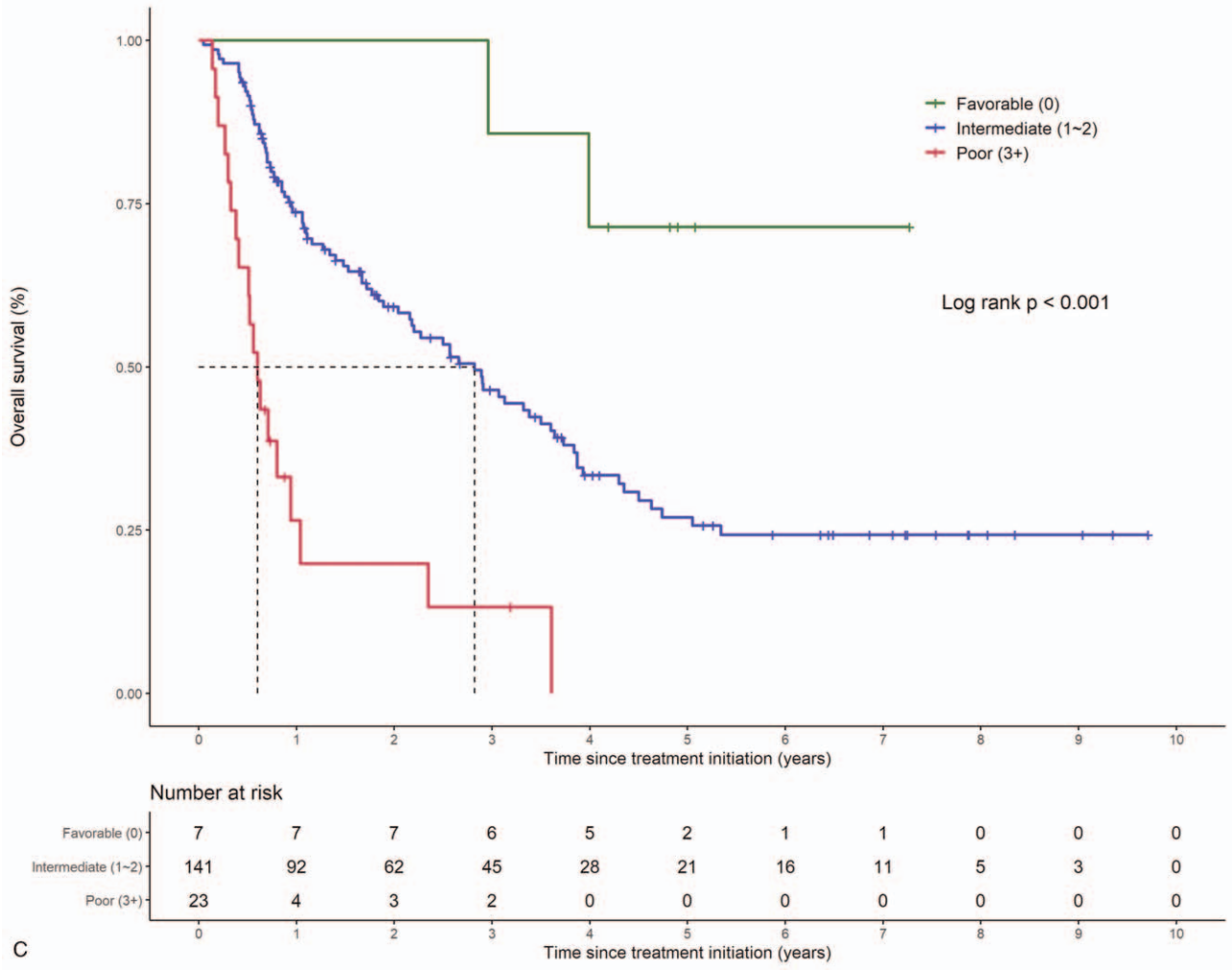

Figure 2. (Continued).

Table 4

Measures of model fit from metastatic renal cell carcinoma prognostic models.

External validation cohort	Akaike information criterion	Concordance-index (Standard error)	Generalized R^2
KRoCS	922.4	0.69 (0.03)	0.22
MSKCC	925.0	0.67 (0.03)	0.19
IMDC	944.5	0.62 (0.03)	0.11
Model-developing cohort	**Akaike information criterion**	**Concordance-index (Standard error)**	**Generalized R^2**
KRoCS	4079.0	0.71 (0.03)	0.22
MSKCC	1453.9	0.69 (0.03)	0.22
IMDC	4114.5	0.68 (0.03)	0.18

KRoCS = Korean Renal Cancer Study Group, MSKCC = Memorial Sloan Kettering Cancer Center, IMDC = international metastatic renal cell carcinoma database consortium.

parameters of model fit showed that the new KRoCS model maintains its consistency and distinguishes itself from MSKCC and IMDC models with superiority. We expect this model to be challenged by more cohorts and maintain its validity in further studies. In the near future, we could improve these types of prognostic model using artificial intelligence machine learning technique with larger dataset. Employing prognostic model will enable physicians to anticipate life expectancy of patients with clear cell mRCC and to make more accurate treatment plan for them.

Acknowledgments

We thank Jae Hyung Cha, Ph.D. for providing us statistical consultation.

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