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Development of the clinical calculator for mortality of patients with metastatic clear cell type renal cell carcinoma: An analysis of patients from Korean Renal Cancer Study Group database

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Purpose: To develop the clinical calculator for mortality of patients with metastatic renal cell carcinoma (mRCC) using Korean Renal Cancer Study Group (KRoCS) database.

Materials and Methods: Data from 1,115 patients with mRCC treated in 4 hospitals joining KRoCS between 1993 and 2016 were pooled. Five-year survival rates were calculated using Kaplan–Meier curve. A clinical calculator for 5-year mortality was developed using multivariable logistic regression analysis and validated externally using dataset including 916 patients from 4 other hospitals.

Results: Overall survival rates and cancer specific survival rate at 5 years were 28.5% and 29.4%, respectively. Among baseline factors, increased neutrophil-lymphocyte ratio (≥4), synchronous metastasis, low albumin (<3.0 g/dL), and low hemoglobin (<lower limit of normal: male, 13 g/dL; female, 11.5 g/dL) were the significant factors in 5-year mortality. Good internal validity was demonstrated with area under the curve estimates being 0.774 at 5-year mortality calculation and the calibration plot. In the external validation, 758 (82.8%) died by 5 years among these patients, with the average model-predicted rate of 72.9%.

Conclusions: A clinical calculator has been developed to quantify the risk of death for individual patients after treatment of mRCC. This tool may be useful for patients or their guardians who want to know their prognosis and to identify patients requiring aggressive therapy and additional supportive measures during and after treatment.

Keywords: Carcinoma; Carcinoma, renal cell; Mortality; Prognosis

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INTRODUCTION

Although small renal masses are detected frequently owing to routine screening using ultrasonography or computed tomography (CT), about one-third of patients with localized renal cell carcinoma (RCC) eventually experience disease recurrence or distant metastasis and 15% to 20% of patients with RCC present metastatic disease at initial diagnosis [1,2]. To treat metastatic RCC (mRCC) target therapy with TKI has been the treatment of choice for the last decade, but treating and surveillance of patients faces many limitations today [3]. The patients or their guardians usually ask the physician prognosis of the patient with mRCC, especially how long he or she will live or what the possibility of living up to 5 years is. Assessing patient prognosis is inherently subjective; however, it would be valuable to be able to identify the patients at an increased risk of 5-year mortality.

In addition to limited knowledge of prognostic factors associated with mortality in mRCC, to our knowledge, clinical calculator predicting the likelihood of mortality for a given patient do not exist up to now. Because overall survival (OS) can be highly variable in mRCC, the ability to objectively determine information about an individual patient's likelihood of 5-year survival be helpful to both physician and patients. The aim of this study is to develop the clinical calculator for mortality of patients with mRCC using Korean Renal Cancer Study Group (KRoCS) database.

MATERIALS AND METHODS

1. Description and purpose of the KRoCS database

The KRoCS database contains individual data on patients with metastatic RCC enrolled in 9 hospitals: Korea University Medical Center, Seoul National University Hospital, Asan Medical Center, Samsung Medical Center, Seoul National University Bundang Hospital, National Cancer Center, The Catholic University of Korea, Seoul St. Mary's Hospital, Chonnam National University Hwasun Hospital, Wonkwang University Hospital. It was established based on website system since 2013 to study end points such as progression-free survival and OS, and also to produce major analyses to improve understanding of mRCC. The KRoCS database comprises of patient demographics, TNM stage and pathology type of synchronous/metachronous metastasis case, laboratory results and drug agent of first-line/second-line/third-line treatment, the details of additional treatment/presurgical therapy and follow-up data.

2. Study population

We retrospectively analyzed from 1,115 patients with clear cell type mRCC who treated with first-line target agent in 4 hospitals such as Asan Medical Center, Samsung Medical Center, National Cancer Center, The Catholic University of Korea, Seoul St. Mary's Hospital between 1993 and 2016. Descriptive statistics for patient, disease, and treatment characteristics as well as mortality rates at 5-year were computed. For prognostic modeling, patient factors were evaluated for possible associations with mortality including age at first-line target agent administration, sex, body mass index (BMI, kg/m^2) at time of treatment, performance status (Eastern Cooperative Oncology Group, ECOG; 0, 1, 2+), presence of distant metastasis at initial RCC diagnosis, number of metastatic sites, pathologic T stage, Fuhrman nuclear grade, routine laboratory studies including complete blood count, prothrombin and partial thromboplastin times, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase, lactate dehydrogenase, blood urea nitrogen, calcium, total protein, albumin, presence of previous nephrectomy and metastasectomy, disease-free interval following initial target agent, and type of first-line target agent. Pathological staging and histological subtype of RCC specimens were determined using the 2010 version of the American Joint Committee on Cancer TNM system and the Heidelberg recommendations. The nuclear grade of the tumor cells was assessed using the Fuhrman's grading system.

3. Development of clinical calculator for mRCC mortality at 5-year

Five-year OS and cancer specific survival rates were calculated using Kaplan–Meier curve. In order to quantify the impact of the prognostic factors on the 5-year mortality, logistic regression models were used in the same way as in previous study, where significance required both $p<0.05$ and clinically meaningful effects (more than 1.0 of odds ratios [ORs]) [4]. Statistically and clinically significant variables were analyzed with the multivariable logistic regression analysis using the backward stepwise method; variables no longer contributing either statistically or clinically on statistical adjustment were then excluded, resulting in final multivariable models for each time point. Finally, a clinical calculator for mortality at 5-year was developed from the final multivariable model.

As measures of internal validation, the area under the receiver operating characteristic curve and calibration plot were reported. External validation of the nomogram was performed using data set from 4 other hospitals including

Chonnam National University Hwasun Hospital, Korea University Ansan Hospital, Seoul National University Hospital, and Seoul National University Bundang Hospital. 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. Analyses were performed using the IBM SPSS Statistics program version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Patient characteristics and treatment outcomes

Baseline patient demographics, disease characteristics and laboratory results are summarized in Table 1. The median age at systemic treatment was 60 years (interquartile range, 51–67), 78.7% of patients (878/1,115) were male, and 60.0% (669/1,115) had synchronous metastasis. The sites of metastasis are followings; lung (75.1%), lymph node (37.5%), bone (27.2%), liver (13.6%) and brain (7.4%). Forty-two percent of patients (472/1,115) had an ECOG performance status of 0, and 72.8% (812/1,115) had undergone a previous nephrectomy. The type of target agents which were administered to the patients were followings; Sunitinib (673, 60.4%), Sorafenib (150, 13.5%), Pazopanib (222, 19.9%), Everolimus (15, 1.3%), Temsirolimus (22, 2.0%). The overall response rate for these 1,115 patients was 28.0% (312/1,115), which included 139 survivors who lived for 3 years or longer and 85 survivors who lived for 5 years or longer.

2. Development of clinical calculator for mRCC mortality at 5-year

The median follow-up period the survivors was 26.7 months (range, 0.9 to 357 months). Seven hundred twenty-three (64.8%) of the 1,115 patients confirmed to be dead. OS rate was 28.5%, and cancer specific survival rate was 29.4% at 5 years. The median OS was 30 months (95% confidence interval [CI], 27 to 33 months) and 5-year OS rate was 28.5%. In patients with synchronous metastasis, the median OS was 20 months (95% CI, 17 to 22 months) and 5-year OS rate was 17.5%, and in patients with metachronous metastasis, the median OS was 50 months (95% CI, 41 to 58 months) and 5-year OS rate was 43.8%. The median cancer specific survival was 31 months (95% CI, 27 to 34 months) and 5-year cancer specific survival rate was 29.4%. In patients with synchronous metastasis, the median cancer specific survival was 20 months (95% CI, 18 to 22 months) and 5-year cancer specific survival rate was 17.7%, and in patients with metachronous metastasis, the median cancer specific survival was 53 months (95% CI, 45 to 62 months) and 5-year cancer specific survival rate was 45.9%. In the multivariable logistic regression analysis at 5-year death cases, increased neutrophil/lymphocyte ratio (NLR), synchronous metastasis, low albu-

Table 1. Demographics and disease characteristics of calculator development cohort and external validation cohort

Variable	Calculator development cohort (n=1,115 cases)	External validation cohort (n=916 cases)	p-value
Age at RCC diagnosis (y)	57.4±11.4	58.3±12.0	0.11
Age at systemic treatment (y)	59.5±11.5	60.8±11.8	0.01
Sex			0.49
Male	878 (78.7)	705 (77.5)	
Female	237 (21.3)	205 (22.5)	
Metastasis			<0.001
Synchronous	669 (60.0)	448 (49.3)	
Metachronous	446 (40.0)	460 (50.7)	
Site of metastatic disease			
Lung	837 (75.1)	279 (37.8)	
Lymph node	418 (37.5)	168 (22.7)	
Bone	303 (27.2)	140 (18.9)	
Liver	152 (13.6)	45 (6.1)	
Brain	83 (7.4)	17 (2.3)	
Others	302 (27.1)	90 (12.2)	
ECOG performance status			0.31
0	472 (42.3)	365 (40.1)	
≥1	643 (57.7)	545 (59.9)	
Prior nephrectomy			<0.001
Yes	812 (72.8)	264 (58.9)	
No	303 (27.2)	184 (41.1)	
Hb (g/dL)	12.6±2.2	12.1±2.5	0.002
White blood cell count	6,578.2±2.9	7,926.9±2.7	<0.001
Platelet	209,440±147.4	298,260±108.9	<0.001
Neutrophil	3,847.0±2,335.2	5,394.1±2,535.5	<0.001
Lactate dehydrogenase (U/L)	322.3±222.5	319.8±241.4	0.92
Albumin (g/dL)	3.9±0.6	3.8±0.6	0.34
Serum corrected Ca (mg/dL)	9.1±0.7	9.4±1.0	<0.001
Treatment			
Sunitinib	673 (60.4)	397 (51.9)	
Sorafenib	150 (13.5)	81 (10.6)	
Pazopanib	222 (19.9)	201 (26.3)	
Everolimus	15 (1.3)	26 (3.4)	
Temsirolimus	22 (2.0)	60 (7.8)	

Values are presented as mean±standard deviation or number (%).
RCC, renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group.

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Table 2. Univariable and multivariable logistic regression analysis of patient demographic and clinical characteristics at 5-year mortality

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (male)	0.966 (0.599–1.556)	0.886		
Age at mRCC diagnosis	1.014 (0.995–1.033)	0.162		
ECOG performance status ≥1	1.330 (0.759–2.326)	0.319		
Neutrophil/lymphocyte ratio ≥4	4.160 (1.890–9.157)	<0.001	4.227 (1.958–9.127)	<0.001
Synchronous metastasis	3.245 (2.180–4.831)	<0.001	3.365 (2.274–4.981)	<0.001
No. of metastasis ≥2	1.415 (0.953–2.103)	0.085		
Albumin <3.0 g/dL	2.121 (1.087–4.140)	0.028	2.146 (1.125–4.093)	0.021
Corrected Ca >9.2 mg/dL	1.434 (0.721–2.852)	0.305		
Hb (<LLN, male 13 g/dL, female 11.5 g/dL)	1.802 (1.188–2.733)	0.006	1.830 (1.223–2.739)	0.003
Platelet (>ULN)	0.453 (0.151–1.365)	0.160		
WBC (>ULN)	1.267 (0.565–2.837)	0.566		

OR, odds ratio; CI, confidence interval; mRCC, metastatic renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; LLN, lower limit of normal; ULN, upper limit of normal; WBC, white blood cell.

min, and low hemoglobin (Hb) were proven to be the significant variables (Table 2). The following prediction equation of clinical calculator for mortality for mRCC mortality at 5-year was developed utilizing them and the calculator is available on the website (https://med2sci.net/mrcc);

Probability=exp(-0.203+1.213×synchronous metastasis+0.604×low hemoglobin+1.442×increased NLR+0.763×low albumin)/(1+exp(-0.203+1.213×synchronous metastasis+0.604×low hemoglobin+1.442×increased NLR+0.763×low albumin)).

All the variables in the equation are categorical ones, where 1 is used when the variables are abnormal (synchronous metastasis is identified, Hb level is below lower limit-male 13 g/dL, female 11.5 g/dL, NLR ≥4, albumin <3.0 g/dL) and otherwise 0 is used in the equation.

Good internal validity was demonstrated, with area under the curve estimates being 0.774 at 5-year OS receiver operating characteristic curve and with the calibration plot showing the similar observed versus predicted outcomes across a spectrum of risk groups as shown Fig. 1.

3. External validation of clinical calculator

Demographics and disease characteristics of external validation cohort (total of 916 patients) are shown in Table 1 and external validation results for the 5-year model are shown in Table 3. Among these patients, 758 (82.8%) died by 5 years, with the average model-predicted rate of 72.9% with the 95% CI 44.9% to 96.8%. In addition, within each patient subgroup (defined by the significant variables in the final model), there are similarities between the mean predictive rates and the actual rates (Table 3). All the actual rates fell within the 95% CI of the predictive rate.

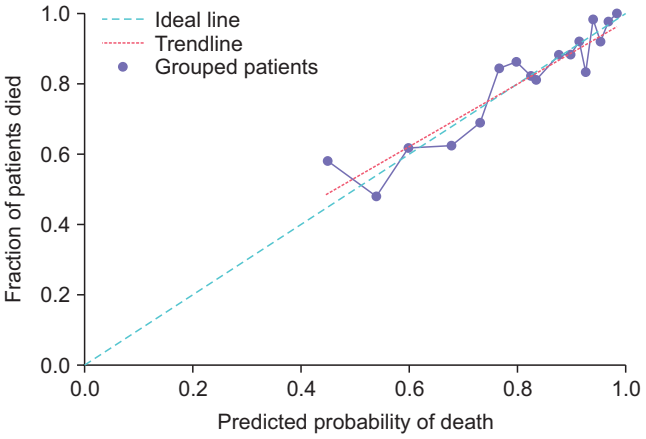

Fig. 1. Calibration plot showing the similar observed versus predicted outcomes across a spectrum of risk groups.

DISCUSSION

There are several efforts to establish nomograms to predict the prognosis of patients with localized RCC after surgery, such as the stage, size, grade and necrosis score (SSIGN) score, the University of California Integrated Staging System (UISS) and Leibovich prognostic score [5-8]. Among them, UISS stratification is the validated prognostic model by the guideline panel and seemed to be the most widely used [9]. On the other hand, in metastatic disease, the first prognostic model was published at the Memorial Sloan-Kettering Cancer Center (MSKCC) in 1999 and they proposed prognostic model of phase III trials using interferon-alpha in 2002 [10,11]. Since then, several institutions have proposed a prognostic model of mRCC, and the prognostic prediction model for systemic treatment in the current guideline is based on the results of the International Metastatic Renal Cancer Database

Table 3. External validation of the calculator for 5-year mortality

Patients group	No.	Mean predictive rate	95% CI	Actual rate
Overall	916	0.7192	0.4494 to 0.9684	0.8280
Neutrophil/lymphocyte ratio				
<4	643	0.7002	0.4494 to 0.8786	0.7994
≥4	184	0.9356	0.8326 to 0.9850	0.9293
Synchronous metastasis				
Absent	462	0.6036	0.4494 to 0.9010	0.7554
Present	448	0.8618	0.7330 to 0.9850	0.8996
No. of metastasis				
<2	379	0.6864	0.4494 to 0.9550	0.7652
≥2	476	0.8005	0.5404 to 0.9850	0.8824
Albumin (g/dL)				
≥3	728	0.7377	0.4494 to 0.9684	0.8132
<3	51	0.9528	0.8219 to 0.9850	0.9804
Hb (g/dL)				
≥LLN (male 13, female 11.5)	372	0.6475	0.4494 to 0.9436	0.7473
<LLN (male 13, female 11.5)	458	0.8321	0.5989 to 0.9850	0.8930

CI, confidence interval; Hb, hemoglobin; LLN, lower limit of normal.

Consortium (IMDC) risk group, which extends the MSKCC 2002 model [12]. IMDC risk group proposed two additional prognostic factors (neutrophil and platelet count) in addition to the four factors (Karnofsky Performance status, time from diagnosis to treatment, Hb, corrected serum calcium) which were proposed by the MSKCC 2002 model.

However, they removed lactic dehydrogenase (LDH) which is included in MSKCC group. Otherwise, the Cleveland Clinic developed a prognostic model based on clinical trial of 120 patients. They concluded that interval from diagnosis to treatment, abnormal baseline corrected serum calcium, ECOG performance status ≥1, neutrophil count greater than 4.5 K/μL, and platelet count greater than 300 K/μL were correlated with poor prognosis [13].

Treatment of mRCC has been changed since targeted agents were introduced and median OS has increased from 10 months in the cytokine era to about 30 months in the targeted therapy era [14]. However, these previous studies and other prognostic tools have been published more than a decade ago and were restricted to the immunotherapy-treated population [10,11,15,16]. Therefore, there has been an effort to make a prognostic model in various studies since 2010. Manola et al. [17] reported prognostic model for predicting the probability of OS for patients with metastatic RCC. They included 8 prognostic variables such as alkaline phosphatase, white blood cell count, interval from diagnosis to treatment, Hb, LDH, corrected Ca, performance status and serum albumin as independent predictive factors of prognosis. In addition, Shinohara et al. [18] presented in their analysis of 361 patients with previously untreated metastatic RCC that two clinical characteristics (interval from diagnosis to treatment, synchronous metastasis) and 2 biochemical factors (Hb, LDH) were revealed as prognostic factor of OS. The previous studies are summarized in Table 4 [10-12,15-18].

Despite these various models, the factors predicting each survival are different. These differences may be the result from the heterogenicity of each race, study design, and treatment regimen. In addition, most of previous prognostic models for metastatic RCC were developed using data from European and USA patients. For example, as the result of study by Naito et al. [19] and Shinohara et al. [18], the median OS of Japanese patients with metastatic RCC treated with cytokine therapy was about 2 years, which appeared to be markedly longer than that in Western studies. In addition, OS of our study was 30 months, which was longer than that of Western studies as well as that of previous Japanese studies. Therefore, it is unclear that whether prognostic models reported from Western were applicable to all Asian patients.

The final model presented in this study is consisted of one clinical and three laboratory values that are readily available and that have been described to be associated with survival outcomes. The present study shows that NLR (≥4), anemia, low albumin level (<3.0 g/dL), and presence of synchronous metastasis are important factors indicating poor prognosis and associated with the decreased OS. The differences in clinical parameters reported among the studies may reflect the specific factors examined and how they were classified or defined, differences in methodology, and specific patient populations studied. Because mRCC has poor OS,

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Table 4. Laboratory and clinical prognostic factors in the prognostic models for metastatic RCC

Prognostic model	Authors	Country	Year	Median OS (mo)	Prior Nx.	Alb	ALP	Hb	LDH	cCa	CRP	Neutrophil count	Platelet count	PS	DFI	Synchronous metastasis	No. of metastasis	Bone metastasis	Prior treatment
MSKCC model	Motzer et al. [11]	USA	1999	10	○			○	○	○				○					
MSKCC 2002 model	Motzer et al. [10]	USA	2002	13		○	○	○	○	○				○	○				
French mode	Négrier et al. [16]	France	2002					○			○				○		○		
CCF model	Mekhail et al. [15]	USA	2005	14.8				○	○	○							○		RTx
IMDC Model	Heng et al. [12]	USA, Canada	2009	22				○		○		○	○	○	○				
IKCWG model	Manola et al. [17]	USA, Canada, Israel	2011	11			○	○	○	○		○ (WBC)		○	○		○		Immunotherapy
JMRC model	Shinohara et al. [18]	Japan	2012	26				○	○						○		○	○	
KRoCS model	Park et al. (this study)	Korea	2018	30		○		○				○ (NLR)				○			

RCC, renal cell carcinoma; OS, overall servival; Nx., nephrectomy; Alb, albumin; ALP, alkaline phosphatase; Hb, hemoglobin; LDH, lactic dehydrogenase; cCa, corrected calcium; CRP, C-reactive protein; PS, performance status; DFI, disease-free interval; MSKCC, Memorial Sloan-Kettering Cancer Center; CCF, Cleveland Clinic Foundation; IMDC, International Metastatic Renal Cancer Database Consortium; IKCWG, International Kidney Cancer Working Group; JMRC, Japanese Metastatic Renal Cancer; KRoCS, Korean Renal Cancer Study Group; RTx, radiotherapy; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio.

unlike other previous studies, we performed the stratification of 5 years survival. By analyzing and combining these four variables, we developed a clinical calculator of patients with mRCC. The validity of this prognostic calculator was confirmed by internal validation and external validation using data from other four selected institutions across South Korea.

Compared with the previous studies, one of the notable finding of this study is that low serum albumin level was correlated with poor prognosis in mRCC patients. Except MSKCC 2002 model proposed by Motzer et al. [10], serum albumin was not noted as prognostic factors in patients with mRCC. However, the preoperative nutritional status of patients including albumin level is not only associated with the postoperative complications, but also with the long-term outcomes of patients with malignant tumors include RCC [20-22]. Cancer cachexia, which is manifested by decrease in albumin, is triggered by a sustained inflammatory response, either by tumor itself or by host response. Additionally, cancer cachexia may be the factor in mRCC patients failing to tolerate target therapy [23]. Because Asian people are smaller than Westerners, weight loss or nutrition status due to cancer can be relatively more affected. For this reason, the serum albumin level in this cohort seems to be closely related to the prognosis of OS compared with other previous studies.

NLR was revealed as independent prognostic value in our study instead of neutrophil count. Recently, numerous investigators suggested that NLR was emerged as a survival prognostic factor in RCC. Especially in a large European non-metastatic RCC cohort study, NLR was revealed as an independent prognostic factor for OS [24]. In addition, Motzer et al. [25] also suggested in their large placebo-control study that benefit of adjuvant sunitinib over placebo was observed across subgroups including NLR below 3. However, few large cohort studies have investigated the value of NLR prognostic factors in mRCC. Some previous investigators presented that preoperative NLR elevation is significantly associated with poor outcomes in patients with mRCC; however, the number of patients analyzed in that study was less than one hundred patients [26,27].

The Karnofsky performance status score was used in the previous studies to assess the patient's performance status, whereas the present study used ECOG performance status. While both performance scales are useful in assessing the performance of cancer patients, the ECOG scale is often preferred for its simplicity and intraobserver reproducibility [28]. Many previous reports demonstrated that performance status was independent risk factor of survival in mRCC [5,12]. However, poor performance scale was not revealed as independent risk factor of 5-year mortality in our study. This result suggests that subjective factors among clinicians evaluating performance scale may act as a bias. In addition, genetic heterogeneity may result in different outcome, since previous studies mostly targeted western populations, whereas this study only targeted Asian population.

Regarding the most widely used system is the MSKCC model, external validation of this risk classification was performed by the Cleveland Clinic Foundation group and its appropriateness has been confirmed [15]. However, compared with the previous prognostic model, the concordance index of 0.729 achieved by this model in the validation data set was very similar to the bias-adjusted concordance statistic of 0.73 reported by Heng et al. [12] although our model does not include disease free interval, performance status, platelet and corrected Ca. This suggests that our model can be more accurate than IMDC or MSKCC model when applying to Asian, especially Korean.

However, there are several limitations which should be addressed. This is the retrospective multicenter study that has potential risks of heterogeneous data arising from the lack of a central pathology review as well as from interobserver variability among the different clinicians and radiologists. In addition, as mentioned above, there is potential bias from incomplete data collections for some individual patients. Despite the limitations, the contributions of this multicenter study are as follow. First, to our knowledge, this is the first study developing clinical calculator for mortality of patients with mRCC using Asian cohort. Considering most of the previous studies have evaluated Western populations, it is meaningful that this study is large scale cohort study of Asian population. Second, this study reflects the improved survival outcome of mRCC since 2010. Since the previous articles have been published based on the data before 2010 analyzed, the present study based on the recent data of up-to-date treatment is quite valuable. MSKCC 2002 model presented that OS was 13 months and IMDC risk group study also suggested that OS was 22 months. However, our study suggested that OS of the patients with mRCC was extended up to 30 months and 5-year OS rate was 28.5%. Third, to minimize risk of misclassification and a lack of consistent clinical data collection, one data manager performed to collect all the data from each institution based on consistent criteria.

CONCLUSIONS

The 5-year OS rates in patients with mRCC was 28.5%, with several factors such as increased neutrophil-lympho-

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cyte ratio, synchronous metastasis, low albumin, and low Hb showing significant associations with 5-year mortality. A clinical calculator predicting the probability of mortality at 5 years has been developed to quantify the risk of death for individual patients after systemic treatment of mRCC. This calculator was validated internally with calibration plot and validated externally with another dataset. This validated clinical calculator would be useful for patients or their guardians who want to know their prognosis and for identifying patients requiring aggressive therapy and additional supportive measures during and after treatment. Additionally, identifying the patients with poor prognosis and providing them supportive care effectively also will result in improving the quality of life of the patients.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

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