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Original Article

Prognostic significance of frailty in patients undergoing surgery for renal cell carcinoma and construction of a predictive model

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Abstract: *Purpose:* We evaluated the association between frailty and overall survival (OS) and metastasis-free survival (MFS) in patients with renal cell carcinoma who underwent radical surgery. *Methods:* We performed a retrospective study of patients with histologically confirmed non-metastatic renal cell carcinoma who underwent surgery between January 2004 and July 2014. Frailty was quantified using the Canadian Study of Health and Aging Modified Frailty Index (mFI). Univariate and multivariate analyses were performed to determine the potential prognostic value of frailty. Nomograms were established to evaluate prognosis for OS and MFS. The predictive accuracy of nomograms was measured by Harrell's concordance index (c-index). *Results:* Of the 672 patients identified in this study, patients were divided into 2 groups (mFI < 2 and mFI ≥ 2) based on X-tile program. Patients with an mFI ≥ 2 had significantly poorer OS (p = 0.0006) and MFS (p = *0.0009*) than those with an mFI < 2 in Kaplan-Meier survival analysis. Multivariate analysis identified higher mFI value as an independent risk predictor of overall survival (HR = 2.43; 95% CI = 1.40-4.23; p = 0.002) and metastasis-free survival (HR = 2.22; 95% CI = 1.34-3.69; p = 0.002). Moreover, the nomograms combined with mFI could accurately predict OS (c-index: 0.831) and MFS (c-index: 0.763). *Conclusion:* In our study of non-metastatic renal cell carcinoma, a higher mFI value can effectively act as an independent prognostic predictor of postoperative survival. Additionally, the established nomograms can be applied in prognosis of survival for RCC patients after curative nephrectomy.

Keywords: Frailty, renal cell carcinoma, overall survival, metastasis-free survival, nomogram

Introduction

Renal cell carcinoma (RCC) is one of most common urological cancers worldwide, and accounts for approximately 90% of all kidney malignancies [1-3]. As a result of the development of modern radiologic screening tools, including ultrasonography and computed tomography (CT), there has been an annual worldwide increase of approximately 2% in the incidence of RCC over the last 2 decades [2]. RCC is primarily a disease of older patients, with the peak incidence occurring at the age of 60-70 years [2]. Thus with population growth and aging, the burden of RCC on the health care system will continue to rise.

Approximately 30% of RCC patients are diagnosed with metastases at first diagnosis, and another 20% of localized RCC patients who undergo curative surgery will develop metastases during follow-up [4]. The mortality rate of metastatic RCC is very high, although novel target therapies have been developed [5]. Therefore, determining prognostic predictors to more accurately select RCC patients with poor survival is becoming increasingly clinically important.

Frailty is characterized by age-related decreases in the physiologic reserve, resistance to stressors, and dysregulation in multiple bodily systems, which results in vulnerability to adverse outcomes [6]. Previous studies have demonstrated that frailty is generally correlated with poor survival [6-10]. The first measurement to assess frailty was the Fried Frailty phenotype, which assesses 5 specific manifest

Table 1. Risk factors used to calculate the modified frailty index and incidence in the cohort

Risk factor	Score	No. in cohort
Functional health status before surgery: partially or totally dependent	1	24 (3.6%)
Diabetes mellitus type II	1	159 (23.7%)
Chronic obstructive pulmonary disease	1	57 (8.5%)
Congestive heart failure	1	3 (0.4%)
History of myocardial infarction within 6 months	1	4 (0.6%)
Prior cardiac surgery, percutaneous coronary intervention, or angina within past month	1	21 (3.1%)
Hypertension	1	294 (43.8%)
Impaired sensorium	1	3 (0.4%)
History of transient ischemic attack	1	2 (0.3%)
History of cerebrovascular accident	1	18 (2.7%)
Peripheral vascular disease requiring surgery or active claudication present	1	3 (0.4%)

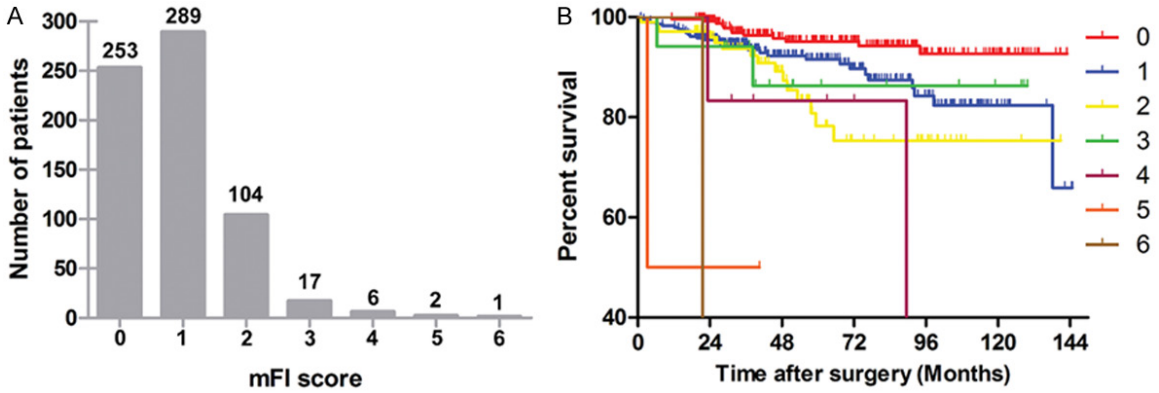

Figure 1. A: Histograms depicting the distribution of the 672 patients with renal cell carcinoma underwent surgery; B: Overall survival versus frailty as measured by mFI score (Log-rank test for trend $p < 0.001$).

indications, including unintentional weight loss, self-reported exhaustion, low physical activity, slowness, and weak grip strength [6]. Subsequently, widely used assessments were created based on a cumulative deficit model and were termed the Canadian Study of Health and Aging Frailty Index (CSHA-FI). This index includes 70 deficits, including clinical signs, symptoms, disease states, and disabilities [11]. However, it is difficult to identify and quantify 70 items for each patient. As a result, a modified frailty index (mFI) was created by mapping the CSHA-FI items to 11 variables that were contained in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database [12, 13]. Findings have shown that mFI accurately predicts long-term survival after femoral neck fracture or glioblastoma resection [14, 15].

The impact of mFI on RCC patients who have undergone curative surgery has yet to be evaluated. Therefore, the objective of the current study was to investigate the mFI as a preoperative predictor of overall survival (OS) and metastasis-free survival (MFS) following surgery, and was first study trying to establish the prognostic nomograms with improved predictive capacity for patients with RCC based on mFI and the clinicopathological factors.

Materials and methods

Patients' selection

After approval from the Institution Ethical Review Board, we retrospectively reviewed the records of consecutive patients with histologically confirmed non-metastatic RCC from January 2004 to July 2014 at the First Affiliated Hospital of Wenzhou Medical University, China. The exclusion criteria were patients who: (I) were younger than 18 years old, (II) had any history of other cancers, (III) underwent pallia-

Table 2. Baseline demographics stratified by modified frailty index

Factors	mFI = 0	mFI = 1	mFI = 2	mFI ≥ 3	*P* value
N	253 (37.6)	289 (43%)	104 (15.5)	26 (3.9%)	
Follow-up	66.8 ± 35.2	56.0 ± 34.0	52.4 ± 30.1	58.4 ± 38.7	*P* = 0.028
Age (SD)	56.2 (12.3)	63.9 (11.8)	66.5 (10.7)	71.4 (10.0)	< 0.001
Sex					
Female	109 (43.1%)	103 (35.6%)	29 (27.9%)	8 (30.8%)	0.04
Male	144 (56.9%)	186 (64.4%)	75 (72.1%)	18 (69.2%)	
ASA grade					
I	46 (18.2%)	34 (11.8%)	6	0	< 0.001
II	204 (80.6%)	235 (81.3%)	83	18	
III	3 (1.2%)	20 (6.9%)	15	8	
BMI (SD)	22.8 (3.3)	23.3 (2.8)	23.8 (2.7)	23.5 (3.2)	0.033
Mean tumor size (IQR)	4 (3-6)	4 (3-6)	4 (3-5.4)	3 (2.5-4)	0.937
Pathological T stage					
pT1	202 (79.9%)	223 (77.2%)	79 (76.0%)	19 (73.1%)	0.075
pT2	32 (12.6%)	25 (8.7%)	16 (15.4%)	5 (19.2%)	
pT3	16 (6.3%)	38 (13.1%)	7 (6.7%)	1 (3.8%)	
pT4	3 (1.2%)	3 (1.0%)	2 (1.9%)	1 (3.9%)	
Fuhrman grade					
1	83 (32.8%)	92 (31.8%)	30 (28.9%)	8 (30.8%)	0.950
2	106 (41.9%)	120 (41.5%)	49 (47.1%)	10 (38.4%)	
3	56 (22.1%)	67 (23.2%)	23 (22.1%)	6 (23.1%)	
4	8 (3.2%)	10 (3.5%)	2 (1.9%)	2 (7.7%)	
Histologic subtype					
Clear cell	220 (87.0%)	250 (86.5%)	91 (87.5%)	26 (100%)	0.500
Papillary	15 (5.9%)	17 (5.9%)	10 (9.6%)	0	
Chromophobe	17 (6.7%)	20 (6.9%)	2 (1.9%)	0	
Collecting duct	1 (0.4%)	1 (0.3%)	1 (1.0%)	0	
Unclassified	0	1 (0.4%)	0	0	

tive surgery instead of curative radical or partial nephrectomy, (IV) underwent kidney transplantation before surgery or had only 1 kidney, (V) had bilateral RCC. All surgeries were performed by 7 surgeons and assessed by 2 professors in our department. The quality of surgeries was considered to be satisfactory.

Preoperative investigations

Referring to our prospectively maintained computer database, the following data were retrieved retrospectively: patient demographic features, past and personal histories, clinicopathological characteristics, and treatment methods. The tumors were pathologically staged and histologically subtyped based on the Union for International Cancer Control seventh TNM classification, the American Joint Committee on Cancer guidelines, and the Heidelberg recommendations [16, 17]. Tumor grading was assessed according to the Fuhrman's grading system [18].

Follow-up strategies

The routine follow-up consisted of blood and urine tests, and chest and abdominal CT or magnetic resonance imaging every 3 to 6 months for the first 2 years after surgery and annually thereafter. Information on death was obtained from outpatient medical records, telephone interview, or the patient's social security death index. The cutoff of follow-up was September 1, 2016. OS and MFS were calculated from the date of surgery to the date of death from any cause, or recurrence of radiologically or histologically confirmed distant metastasis on the date of the last follow-up, respectively. The primary endpoint of this study was OS.

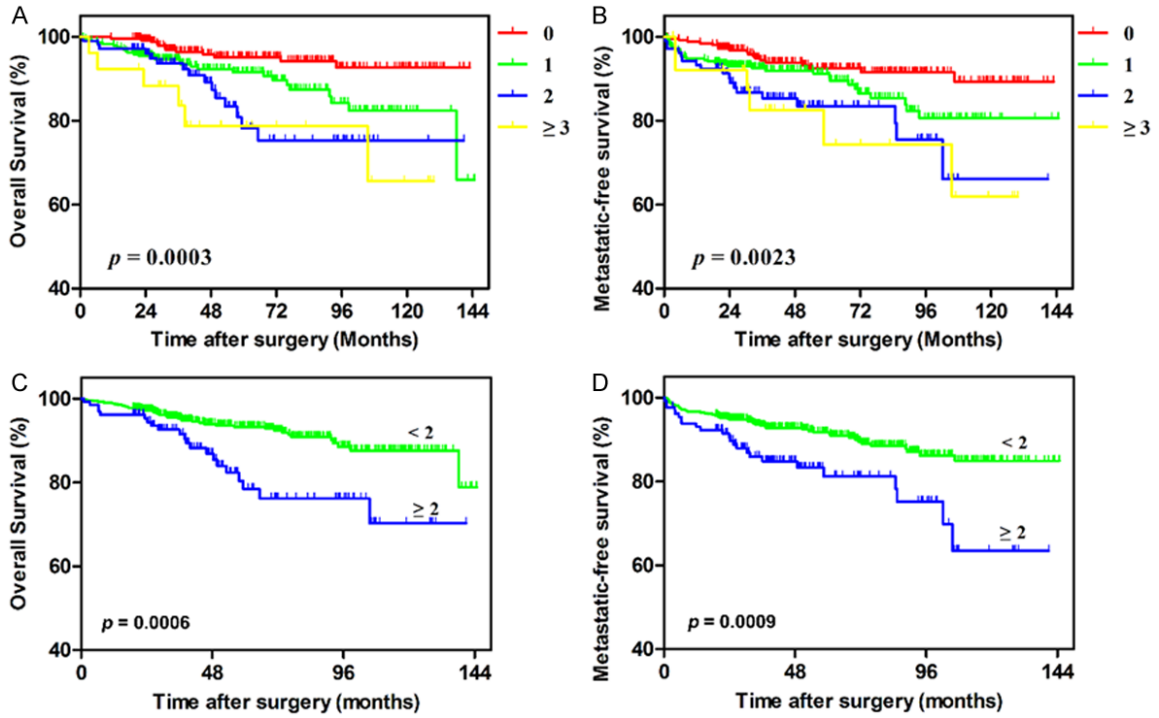

Figure 2. Kaplan-Meier survival curves for OS and MFS versus frailty with patients grouped by (A) and (B) frailty group (mFI = 0, mFI = 1, mFI = 2, mFI ≥ 3), and by (C) and (D) mFI score (mFI < 2, mFI ≥ 2).

Assessment of frailty

Frailty was qualified using the mFI (**Table 1**) [12, 13]. Briefly, it was calculated based on 11 variables from the CSHA-FI, and 1 point was given for each variable based on the functional health status before surgery. The variables were: partially or totally dependent, diabetes mellitus type II, hypertension, chronic obstructive pulmonary disease, congestive heart failure, history of myocardial infarction within 6 months, prior cardiac surgery, percutaneous coronary intervention, or angina within the past month, impaired sensorium, history of transient ischemic attack, history of cerebrovascular accident, and peripheral vascular disease requiring surgery or active claudication present. Ultimately, the mFI scores ranged from 0 to 6 (**Figure 1**).

Statistical analysis

Statistical analyses were performed using the SPSS software package version 22.0 (IBM, Armonk, NY). Normally distributed continuous variables are presented as mean ± standard deviation, and non-normally distributed continuous variables are presented as median and interquartile ranges. Categorical variables are presented as counts and percentages. The association between the mFI and several parameters was compared using the Student's t test, Chi-square test or Fisher's exact test (categorical data), and the Mann-Whiney U test (non-normally distributed continuous data and ranked data). X-tile software (Version 3.6.1, Yale University, New Haven CT, USA) was applied to calculate the discriminatory ability of mFI to identify the optimal cutoff value. The influence of mFI scores on patient OS and MFS was analyzed using the Kaplan-Meier method, and the log-rank test was used to assess the differences. Univariate and multivariate analysis (forward stepwise method) was performed to identify the influence of patient age, sex, BMI, ASA grade, tumor size, pathologic T stage, tumor grade, histologic subtype, and frailty on OS and MFS. Variables with $p < 0.05$ in the univariate analysis were included in the subsequent multivariate analysis. Nomograms for OS and MFS were established by R software (Version 3.4.1; Institute for Statistics and Mathematics, Vienna, VIC, Austria). The predictive accuracy of the two models, of which one included variables only and the other included variables plus mFI, were evaluated by Harrell's concordance index (c-index). All tests were two-

Table 3. Univariate and multivariate logistic regression analysis of risk factors for OS and MFS

OS	Univariate analysis	Multivariate analysis
	HR (95% CI), *P* value	HR (95% CI), *P* value
Sex (male)	1.59 (0.91-2.78), 0.107	
Age (≥ 65)	4.05 (2.22-7.36), < 0.001	3.15 (1.71-5.80), < 0.001
mFI (≥ 2)	2.45 (1.44-4.15), < 0.001	2.43 (1.40-4.23), 0.002
ASA grade (≥ III)	3.31 (1.75-6.25), < 0.001	
BMI (≥ 25)	0.28 (0.11-0.69), 0.006	0.27 (0.12-0.69), 0.006
Mean tumor size (≥ 7)	2.85 (1.69-4.81), < 0.001	2.00 (1.16-3.47), 0.013
Pathological T stage (≥ 3)	4.40 (2.50-7.72), < 0.001	3.94 (2.17-7.17), < 0.001
Fuhrman grade (≥ 3)	2.92 (1.76-4.83), < 0.001	2.27 (1.36-3.78), 0.002
Histologic subtype (Clear cell)	1.48 (0.75-2.91), 0.259	
MFS	Univariate analysis	Multivariate analysis
	HR (95% CI), *P* value	HR (95% CI), *P* value
Sex (male)	1.70 (1.02-2.85), 0.042	
Age (≥ 65)	2.65 (1.63-4.31), < 0.001	2.16 (1.31-3.55), 0.003
mFI (≥ 2)	2.23 (1.37-3.63), < 0.001	2.22 (1.34-3.69), 0.002
ASA grade (≥ III)	2.16 (1.11-4.20), 0.024	
BMI (≥ 25)	0.32 (0.15-0.69), 0.004	0.33 (0.15-0.73), 0.006
Mean tumor size (≥ 7)	2.77 (1.72-4.47), < 0.001	2.11 (1.28-3.49), 0.003
Pathological T stage (≥ 3)	3.33 (1.93-5.74), < 0.001	2.82 (1.59-4.99), < 0.001
Fuhrman grade (≥ 3)	2.59 (1.64-4.09), < 0.001	2.05 (1.29-3.27), 0.002
Histologic subtype (Clear cell)	1.31 (0.69-2.49), 0.409	

sided, and differences were considered to be statistically significant at $p < 0.05$.

Results

Patient grouping

From January 2004 to July 2014, a total of 672 patients, including 249 (37.1%) women and 423 (62.9%) men, were included in our study. The mean age at surgery was 61.7 (12.6) years, and the median tumor size was 4 (range, 3-6) cm. The mean follow-up duration was 59.6 ± 34.5 months. The patients' clinicopathologic characteristics are summarized in **Table 2**. A total of 253 (37.6%) patients had an mFI of 0, 289 (43.0%) had an mFI of 1, 104 (15.5%) had an mFI of 2, and 26 (3.9%) had an mFI ≥ 3 (**Figure 1**). A higher mFI was correlated with sex ($p = 0.04$), BMI ($p = 0.033$), and ASA grade ($p < 0.001$). Patients with higher mFI scores were more likely to be older, the mean age was 56.2 for mFI = 0, 63.9 for mFI = 1, 66.5 for mFI = 2, and 71.4 for mFI ≥ 3. There was no significant difference in the tumor size ($p = 0.937$), pathologic T stage ($p = 0.075$), tumor grade ($p = 0.950$), and histologic subtype ($p = 0.500$) among the mFI groups.

Association of frailty with survival

During follow-up, 74 (11.0%) patients experienced distant metastasis and 61 (9.1%) died within 10 years of follow-up. The 5-year survival rates were 90.5% for OS and 89.7% for MFS, respectively. The optimal cutoff value for mFI of OS was identified as 2 by means of X-tile program (Figure S1), the *P* value of mFI was 0.0009. Therefore, patients were divided into 2 groups: a higher mFI group (mFI ≥ 2) and a lower mFI group (mFI < 2). Patients with an mFI ≥ 2 had significantly poorer OS ($p = 0.0006$) and MFS ($p = 0.0009$) than those with an mFI < 2 in Kaplan-Meier survival analysis (**Figure 2**).

Univariate and multivariate analysis revealed that a higher mFI was a statistically significant predictor of OS and MFS. Therefore, multivariate analysis for OS and MFS was applied to identify various independent predictors (**Table 3**). The following factors were included in the multivariate Cox proportional hazards model: sex, age, mFI value, ASA grade, BMI, tumor size, pathologic T stage, and Fuhrman grade. The results indicated that a higher mFI was an independent risk factor for OS (HR = 2.43, $p = 0.002$) and MFS (HR = 2.22, $p = 0.002$).

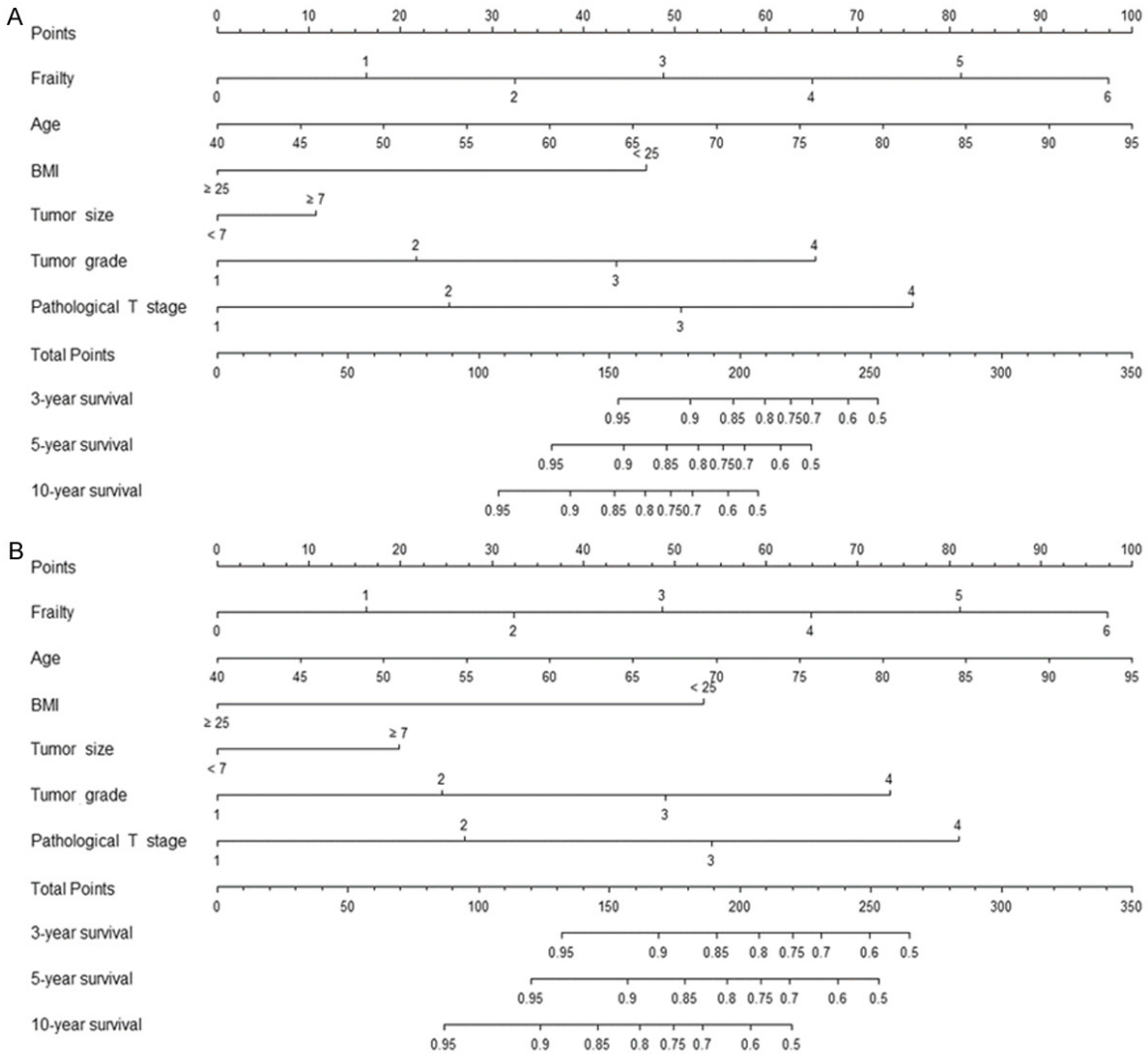

Figure 3. Postoperative nomogram with mFI and significant clinicopathologic characteristics predicted the probability of RCC for (A) OS and (B) MFS. To use the nomogram, an individual RCC patients' value is located on each variable axis, and a line is depicted upward to determine the number of points received for each variable value. Subsequently, the sum of these number is located no Total Point axis, and a line is drawn downward to the survival axes to determine the likelihood of 3-, 5- and 10-year survival of OS or MFS.

Moreover, age, BMI, tumor size, pathologic T stage and Fuhrman grade were also independent predictors of OS and MFS.

Prognostic nomograms for OS and MFS

Prognostic nomograms were depicted by all the independent indicators in the multivariate analysis and were applied to predict the survival rates for RCC patients after surgery (**Figure 3**). To use nomograms, an individual patient's value was located on the variable axis, and each subtype was assigned a score according to the point scale. Then the sum of the points was located on the Total points axis, we could easily draw downward a straight line to the survival axes to determine the estimated probability of survival. These nomograms could predict the probability of death for all-cause or distant metastasis for RCC patients within 3-, 5- and 10-years after surgery (Figure S2). The c-index for OS and MFS were 0.831 and 0.763, respectively.

Discussion

As the incidence of RCC continues to rise, it is important to identify those patients at high risk of a poor prognosis after surgery. In the present study, we used a frailty index to examine the

effects of frailty on long-time survival in RCC patients undergoing surgery. In addition, nomograms were established to improve the predictive accuracy. We found that a higher frailty score (mFI ≥ 2) was an independent risk predictor of OS and MFS, and the predictive nomograms, integrating mFI and other independent factors, could be used for the prognosis and clinical decision-making for surgeons.

Frailty was defined as vulnerability to adverse health outcomes and/or death following stress events [6]. Both kidney cancer and curative nephrectomy are major physiologic stressors, suggesting the potential of assessing frailty in patients with RCC. Therefore, the incorporation of a frailty measurement for older cancer patients has been advocated. The mFI is a simple and efficient frailty assessment tool that has abbreviated from the CSHA-FI [12, 13]. It uses readily available historical variables that can be consistently and reliably collected in the preoperative setting. Thus, the mFI is an ideal screening tool in the everyday clinical setting.

In the current study, our findings demonstrate that higher frailty value is independently associated with declines in OS and MFS. Furthermore, patients with an mFI ≥ 2 had significantly poorer 5-year OS and MFS compared with patients with an mFI < 2. Limited studies have indicated that compared with healthy individuals, frail patients had higher risks of death in several models of frailty. Clough-Gorr et al. illustrated the association between frailty and all-cause mortality at 5, 7 and 10 years of follow-up in older breast cancer patients (adjusted 5-year HR = 1.87, 95% CI 1.36-2.57; adjusted 7-year HR = 2.31, 95% CI 1.40-2.94; adjusted 10-year HR = 1.74, 95% CI 1.39-2.18) [10, 20]. Patal et al. demonstrated that the mFI was associated with mortality both 1 and 2 years after sustaining a femoral neck fracture in patients aged 60 years and over [14]. Additionally, Cloney et al. found that frailty was associated with decreased OS for glioblastoma patients undergoing craniotomy [15]. Therefore, our results are consistent with other frailty studies performed in multiple settings [6, 10, 14, 15, 19].

With the evidence linking frailty to poor outcomes, it has been suggested that frailty assessment should be implemented in clinical practice. Instead of being an irreversible state, frailty occurs as a dynamic process with transitions between higher and lower states of frailty [20, 21]. Therefore, incorporation of the notion of frailty into the clinic to monitor and manage the population health may prevent further deterioration in physical and functional impairment. The management strategies include building frailty clinics for an in-depth assessment and incorporating physical and cognitive exercise, social support, and nutrition for people in the earlier stages of frailty [20, 22, 23]. These strategies may improve the long-term survival of frail patients.

Nomogram has the ability to simplify complicated statistical predictive models into simple graphical representations that generates a numerical probability of a clinical event. Therefore, previous studies have reported that nomograms are more favorable for predicting outcomes in cancers than conventional TNM staging systems [24, 25]. In the present study, we first established and externally validated new nomogram models consisting of mFI, age, BMI, tumor size, tumor grade and pathological T stage, which could predict the probability of die for all-cause and distant metastasis for postoperative patients within 3-, 5- and 10-year. The nomograms performed well in predicting OS (c-index: 0.831) and MFS (c-index: 0.763). These results demonstrated that nomograms could accurate predict prognosis in RCC patients after surgery.

Our study has several limitations. First, it is a retrospective study of a single-institution database, and we acknowledge that patients' medical records may have been incomplete. It is possible that the frailty index and the study results may be influenced if 1 or more deficits in the 11 variables were missed. Therefore, to try to offset this, patient information was confirmed in a telephone interview and patients who were lost to follow-up were excluded from the study. Second, the mFI is well-known to be associated with poor short-term outcomes in older patients; however, its effects on long-term survival have not been widely studied [15, 26, 27]. Finally, frailty was identified as a factor of malnutrition status, while we failed to include the nutritional screening systems, such as nutrition risk index (NRI), nutritional risk screening (NRS-2002), and malnutrition universal screening tool (MUST), because these screen-

ing systems were required to be assessed prospectively.

A higher mFI score (mFI ≥ 2) was revealed as a significant prognostic factor for postoperative long-term survival in patients with non-metastatic RCC. Additionally, the predictive nomograms combined with mFI could be used for the prognosis and clinical decision-making for surgeons.

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Disclosure of conflict of interest

None.

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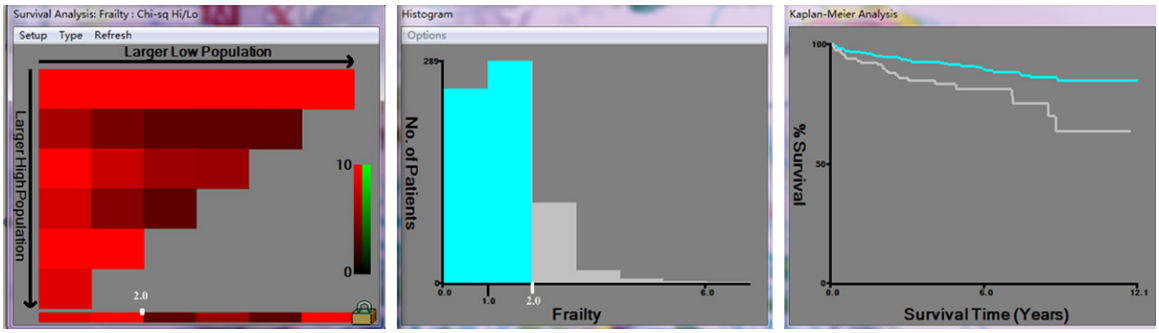

Figure S1. X-tile analyses of overall survival were performed using patients' data to determine the optimal cutoff values for mFI. The sample of RCC patients was divided into the lower mFI group and higher mFI group. X-tile plots of lower mFI group and were shown in the left panels. The optimal cutoff values highlighted by the white lines in the left panels are shown in histograms of the entire cohort (middle panels), and the Kaplan-Meier plots are displayed in the right panels. The optimal cutoff values for mFI was 2 (X^2 = 10.938, *P* = 0.0009).

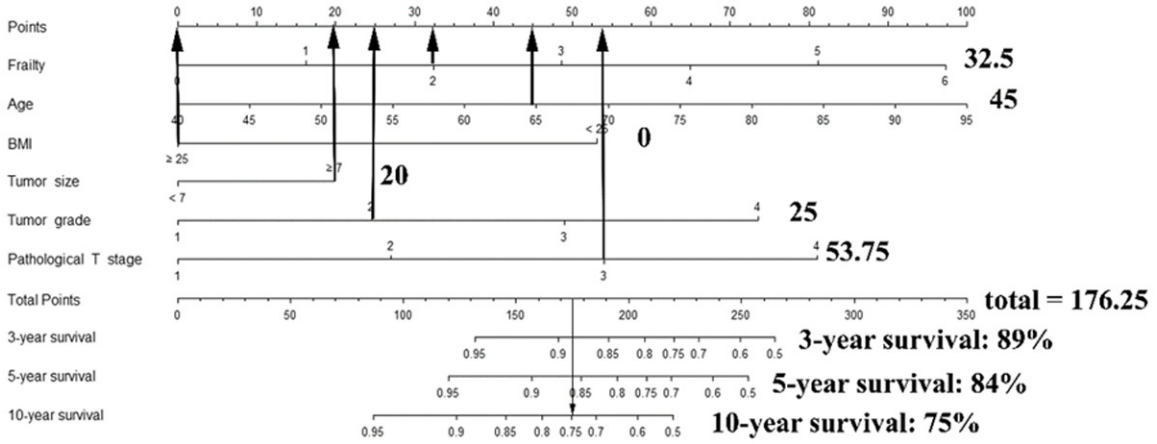

Figure S2. Example for nomogram predicting the probability of 3-, 5- and 10-year MFS in RCC patients. A RCC patients was 65 (score ≈ 45) years old, with mFI = 2 (score ≈ 32.5), BMI ≥ 25 (score = 0), tumor size ≥ 7 (score ≈ 20), tumor grade = 2 (score ≈ 25), and pathological T stage = 3 (score ≈ 53.75). The total risk score for him was 45+32.5+0+20+25+53.75 = 176.25; total score = 176.25 is equivalent to a probability of approximately 89% for 3-year survival, 84% for 5-year survival, and 75% for 10-year survival.