Risk Factors and Oncologic Outcomes for Clinical T1 Renal Cell Carcinoma Upstaging to Pathological T3a and The Construction of Predictive Model: A Retrospective Study

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Purpose: The study is intended to identify the independent predictors of clinical T1 (cT1) renal cell carcinoma upstaging to pathological T3a (pT3a) and construct the predictive nomogram model.

Methods: The data of cT1 renal cell carcinoma was collected from patients who were treated in the Second Hospital of Tianjin Medical University from January 2010 to December 2016. Mann–Whitney U and chi-square tests were performed to analyze continuous and categorical variables respectively. Univariate and multivariate logistic regression were used to identify the predictors of upstaging. Kaplan-Meier method, log-rank test and Cox regression were performed to analyze survival materials.

Results: Among 1,376 cT1 renal cell carcinoma patients, 75 patients were observed upstaging to pT3a, accounting for 5.5%. There were 6 potential predictors of upstaging, i.e age, clinical symptom, tumor size, Fuhrman grade, tumor necrosis and tumor edge regularity. The 5-year recurrence free survival probabilities of upstaging and non-upstaging patients were 73.3% and 91.1%, respectively and upstaging was an independent predictor of recurrence free survival. Two predictive nomograms were constructed and the C-index of them were 0.842 and 0.806, and the calibration curve and decision curve analysis showed highly clinical accuracy of the nomograms.

Conclusion: Two nomogram models were built to predict the probability of cT1 renal cell carcinoma upstaging to pT3a with highly accuracy and specificity. Upstaging was an independent risk factor of recurrence free survival for cT1 renal cell carcinoma patients.

Keywords: Carcinoma, renal cell; upstaging; recurrence free survival; risk factor; nomogram

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2–3% of all human cancers, and it has become the third most common genitourinary malignancy[(1)]. Most cases lack symptoms such as abdominal pain, haematuria or abdominal masses, as the majority RCCs are incidental findings on abdominal imaging, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Nowadays, the clinical diagnosis of RCC relies heavily on a triphasic CT scan, as it has high sensitivity and specificity for determination of the size, location and staging of tumor.

In the guidelines of NCCN and EAU 2021, nephron sparing surgery (NSS) is recommended for treatment of T1 RCC, which provides similar long-term oncologic outcomes as radical nephrectomy (RN). NSS is also indicated for some technically feasible T2 RCC patients, such as bilateral renal tumors, isolated kidney or poor renal function[(2)]. However, the first choice for T3a RCC is RN. Previous studies have shown that the sensitivity and specificity of imaging tests for RCC vary significantly[(3)]. With the development of clinical and pathological staging of RCC, it has become not rare for cT1 RCC upstaging to pT3a. It is difficult to determine the stage of RCC accurately only by preoperative imaging for some T1 cases, and previous literature offers conflicting results regarding the associated factors and prognosis for pT3a upstaging[(4-8)].

Therefore, risk factors and prognosis of pT3a upstaging are of vital importance for clinical treatment. Our study is intended to investigate the risk factors and oncologic outcomes for cT1 RCC upstaging to pT3a, and construct predictive nomogram models of upstaging. As far as we know, the existing predictive model of upstaging are not accuracy enough and no research has included tumor necrosis in CT and tumor edge irregularity in the study. The result of our study found that age, clinical symptom, tumor size, Fuhrman grade, tumor necrosis in CT and tumor edge regularity were independent predictors of upstaging and two nomograms were constructed based on them. Upstaging was an independent predictor of recurrence free survival (RFS) for cT1 RCC patients. Our study included more predictors of upstaging and increased the discrimination and diagnostic efficacy of the nomogram.

MATERIALS and METHODS

Patients and study design

The study was approved by the Institutional Review

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Table 1. Clinical and pathological characteristics of patients by upstage status.

Variable	Non-upstaging (N=1301)	Upstaging (N=75)	*P*-value
Age (years)	57.34 ± 10.88	63.08 ± 10.17	< 0.001
Sex (%) (Male)	923 (70.9)	56 (74.7)	0.489
BMI	25.51 ± 3.27	24.68 ± 3.10	0.492
Side (%) (Left)	672 (51.7)	39 (52.0)	0.953
Smoke (%)	535 (41.1)	32 (42.7)	0.792
Clinical symptom	328 (25.2)	35 (46.7)	< 0.001
Hematuria (%)	126 (38.4)	11 (31.4)	0.161
Abdominal pain （%）	191(58.2)	20 (57.1)	0.006
Abdominal mass (%)	11 (3.3)	4 (11.4)	< 0.001
Hypertension (%)	667 (51.3)	42 (56.0)	0.425
Diabetes (%)	216 (16.6)	15 (20.0)	0.444
Tumor size (cm)	3.95 ± 1.51	5.24 ± 1.35	< 0.001
Tumor exophytic (%)	605(46.5)	31(41.3)	0.383
Nearness to the collecting system or sinus (%)			0.001
≥7mm	394 (30.3)	10 (13.3)	
4-7mm	326 (25.1)	15 (20.0)	
<4mm	581 (44.7)	50 (66.7)	
Necrosis (%)	259 (19.9)	30 (40)	< 0.001
Tumor edge (%) (Irregular)	767 (59.0)	55 (73.3)	< 0.001
Renal sinus compression (%)	692 (53.2)	46 (61.3)	0.171
Histology (%)			0.128[a]
Clear cell	1136 (87.3)	59 (78.7)	
Papillary	45 (3.5)	3 (4.0)	
Chromophobe	52 (4.0)	5 (6.7)	
Others	68 (5.3)	8 (10.7)	
Fuhrman grade (%)			< 0.001
Low grade (I-II)	1204 (92.5)	47 (62.7)	
High grade (III-IV)	97 (7.5)	28 (37.3)	
Type of nephrectomy (%)			< 0.001
NSS	390 (30.0)	6 (7.9)	
RN	911 (70.0)	70 (92.1)	
PSM (%)	18 (1.4)	0 (0) -	

BMI, Body mass index; PSM, Positive surgical margin; NSS, Nephron sparing surgery; RN, Radical nephrectomy.
aFisher's exact test

Board of Tianjin Medical University. A retrospective analysis was performed on 1,376 patients with cT1 RCC who underwent NSS or RN from January 2010 to December 2016, and 1,238 (90.0%) patients were followed up. Both NSS and RN surgeries were performed by open or laparoscopy approach. Clinical and pathological stages were determined by the surgeon according to the preoperative CT or MRI findings, and were confirmed in collaboration with the radiologist and pathologist according to the eighth edition of the TNM Classification of the American Joint Committee on Cancer. PT3a was defined as tumor extension into RV (renal vein) or segmental branches, invasion of pelvicalyceal system, or invasion of PF (perirenal fat) and/or SF (sinus fat) but not beyond Gerota's fascia. Histological subtypes were assessed by Heidelberg classification, and nuclear grading was performed by Fuhrman's grading system. Upstaging was defined as the final pathology at pT3a for cT1 RCC patients. Recurrence was determined by follow-up imaging and/or presence of pathological specimen. The patients were also classified according to the depth of the tumor, and exophytic tumor was defined when ≥ 50% of the tumor protruded externally from the parenchymal surface. Tumor necrosis in CT was defined as low-dense areas of tumor not enhancing during renal contrast-enhanced CT. Tumor edge irregularity was defined as follows: A mass with smooth margin but prominent nodules from part of it, which was defined as "lobular" (**Figure 1A**); and a mass with blurred margin, i.e unclear margin between tumor and renal parenchyma (**Figure 1B**); or a mass with completely irregular margin, regardless of the clarity between tumor and renal parenchyma, with completely non-elliptical shape (**Figure 1C**). Renal sinus compression was defined as direct contact and compression between tumor and collecting system (**Figure 1D**). Evaluation was conducted for patient demographics (sex, age, body mass index (BMI), chronic disease (hypertension, diabetes), clinical symptom (hematuria, abdominal pain, abdominal mass)), type of nephrectomy, imaging (tumor size, tumor necrosis, tumor edge regularity, renal sinus compression) and pathological data (histology, Fuhrman grade, surgical margin status, pathological stage), follow-up duration, site and time to recurrence.

Patients included in the study met the following inclusion criteria (**Figure 2**): (I) Treated surgically in the Second Hospital of Tianjin Medical University without anti-tumor therapy before surgery; (II) Pathologically diagnosed as RCC; (III) With complete imaging data of kidney before surgery, including non-enhanced or contrast-enhanced CT, MRI, etc.; (IV) Tumor size in imaging ≤7cm; (V) With complete clinicopathological data and survival information. The exclusion criteria included: (I) Pathologically diagnosed as non-RCC; (II) Maximum tumor size in imaging ＞ 7 cm; (III) Suffered from other types of cancer; (IV) With RCC history, bilateral RCC or multiple RCCs. (V) With missing clinicopathological, or imaging data; (VI) Underwent renal biopsy or renal radiofrequency ablation without NSS or RN.

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The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Committee Review Board of the Second Hospital of Tianjin Medical University and informed consent was taken from all individual participants.

Table 2. Univariate and multivariate logistic regression analysis of predictors for upstaging to pT3a

Univariate Analysis	OR	95%CI	*P* value	Multivariate Analysis	OR	95%CI	*P* value
Age (continuous)	1.05	1.03-1.08	< 0.001	Age (continuous)	1.05	1.02-1.07	0.001
Necrosis	2.68	1.66-4.34	< 0.001	Necrosis	2.76	1.62-4.72	0.001
Clinical symptom	2.60	1.62-4.16	< 0.001	Clinical symptom	2.19	1.31-3.68	0.003
Nearness to the collecting system or sinus			0.001				
≥7mm	1(reference)						
4-7mm	1.81	0.80-4.09	0.152				
<4mm	3.39	1.70-6.77	0.001				
Tumor edge			0.015	Tumor edge		0.001	
Regular	1(reference)			Regular	1(reference)		
Irregular	1.92	1.13-3.23		Irregular	2.55	1.44-4.52	
Fuhrman grade			<0.001	Fuhrman grade			< 0.001
I-II	1(reference)			I-II	1(reference)		
III-IV	7.40	4.43-12.33		III-IV	5.37	3.05-9.47	
Tumor size			< 0.001	Tumor size			0.001
<4cm	1(reference)			<4cm	1(reference)		
4-7cm	5.56	3.20-9.65		4-7cm	2.97	1.60-5.51	

OR, Odds ratio; 95% CI, 95% Confidence interval.

Statistical Analysis

Continuous variables were described as mean value ± standard deviation, and categorical variables were described as frequency and percentage. Mann-Whitney *U* test was used for the comparison of continuous variables. Chi-square and Fisher's probability test were performed for the comparison of categorical variables. Chi-square test was used when no expected cell count less than 1 and at most 20% of expected cell counts less than 5 and Fisher's exact probability test was used when expected cell count less than 1. In the logistic regression model, the linear relationship between the continuous independent variables and the dependent variable is verified by the Box-Tidwell method. All continuous independent variables have a linear relationship with upstaging. Univariate and multivariable logistic regres-

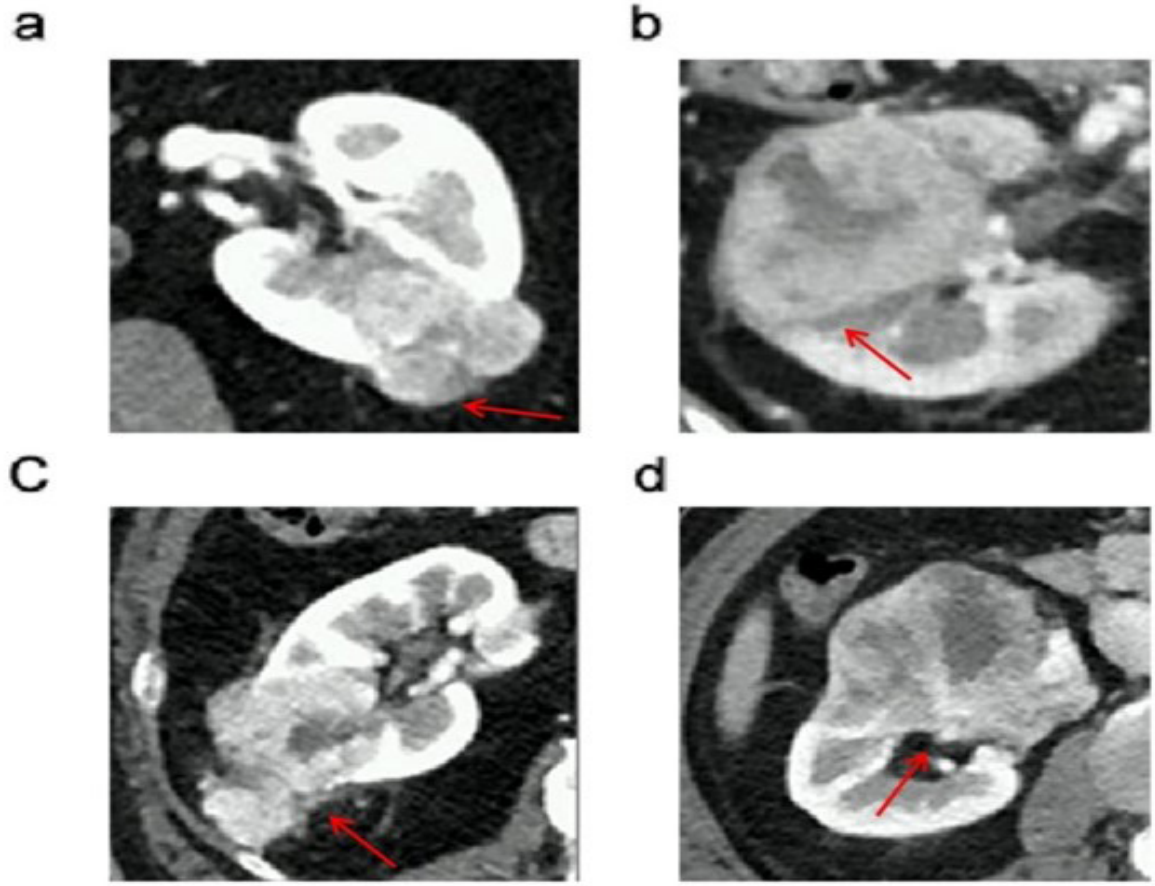

Figure 1. Irregular tumor edge of renal cell carcinoma in contrast-enhanced CT **(A)** A mass with smooth margin and prominent nodules from part of it; **(B)** A mass with blurred margin; **(C)** A mass with completely irregular and non-elliptical shape; **(D)** Renal sinus compression in contrast-enhanced CT

Table 3. Univariate and multivariate Cox regression analysis for predictors of recurrence free survival

Univariate Analysis				Multivariate Analysis			
	HR	**95%CI**	***P* value**		**HR**	**95%CI**	***P* value**
Age (continuous)	1.01	1.00-1.03	0.167				
Sex	0.800						
Male	1.05	0.73-1.51					
Female	1(reference)						
BMI	0.96	0.91-1.01	0.094				
Side	0.104						
Left	0.76	0.55-1.06					
Right	1(reference)						
Smoke	1.03	0.74-1.43	0.874				
Clinical symptom	1.25	0.89-1.77	0.204				
Hypertension	1.08	0.78-1.49	0.665				
Diabetes	1.09	0.71-1.67	0.690				
Necrosis	1.38	0.95-1.99	0.092				
Exophytic	1.02	0.73-1.41	0.921				
Nearness to the collecting system or sinus							
≥ 7mm	1(reference)						
4-7mm	0.96	0.61-1.51	0.855				
<4mm	1.03	0.69-1.53	0.903				
Tumor edge		0.368					
Regular	1(reference)						
Irregular	1.17	0.83-1.64					
Renal sinus compression	0.94	0.68-1.30	0.714				
Histology							
Clear cell	0.77	0.41-1.49	0.428				
Papillary	0.67	0.23-1.95	0.456				
Chromophobe	0.52	0.16-1.66	0.269				
Others	1(reference)						
Fuhrman grade	0.045	Fuhrman grade					0.352
I-II	1(reference)			I-II	1(reference)		
III-IV	1.62	1.01-2.60		III-IV	1.27	0.77-2.09	
Tumor size		0.537					
<4cm	1(reference)						
4-7cm	0.90	0.65-1.26					
Type of nephrectomy		0.727					
NSS	0.94	0.65-1.36					
RN	1(reference)						
Upstage 2.73	1.73-4.31	< 0.001	Upstage	2.55	1.58-4.12	<	0.001

BMI, Body mass index; PSM, Positive surgical margin; NSS, Nephron sparing surgery; RN, Radical nephrectomy; HR, Hazard ratio; 95% CI, 95% Confidence interval.

sion were performed to select independent predictors of cT1 RCC upstaging to pT3a. For the selected predictors, nomogram plots were constructed, and the calibration curve and decision curve analysis were performed. Kaplan-Meier curves and log-rank test were conducted for survival analysis.

The proportional hazard and linearity was validated by cumulative hazard function method for Cox regression and all variables meet the proportional hazard and linearity assumption. Univariate and multivariable Cox proportional hazard models were performed to determine the independent predictor of RFS for cT1 RCC patients. The variable selection algorithm for multivariable logistic and Cox regression analyses was 'Forward Likelihood Ratio'. The follow-up time for survival analysis was from the day of performing the nephrectomy to December 2018. There are 160 RCC patients censored in our study, which accounts for 12.9% of all 1238 RCC patients with survival data. The reasons for censoring include losing contact with patients or their families, patients didn't cooperate with follow-up survey and withdrew from the retrospective study and patients died of any reasons.

We define tumor size as categorical variables when performing logistic and Cox regression analysis, and the cut-off value was 4cm for tumor size. Furthermore, age were regarded as continuous variables when constructing nomogram predictive model. SPSS (version 24) and R software (version 3.5.2) were used for data processing, and statistical significance was defined as p <0.05.

Table 4. Tumor progression of 1238 patients

	Non-upstaging (N=1163)	**Upstaging (N=75)**
Tumor progression	142 (12.2)	22 (29.3)
Local recurrence (%)	56 (39.4)	6 (36.4)
Distant metastasis (%)	86 (60.6)	16 (72.7)
Lung	40	10
Bone	31	4
Retroperitoneal lymph node	21	2
Liver	18	1
Pancreas	17	0
Brain	15	5

Table 5. Multivariate logistic regression of preoperative parameters

Multivariate Analysis	OR	95%CI	*P* value
Age (continuous)	1.05	1.02-1.07	< 0.001
Necrosis	2.64	1.58-4.40	< 0.001
Tumor edge			0.002
Regular	1(reference)		
Irregular	2.36	1.36-4.09	
Clinical symptom	2.40	1.46-3.94	0.001
Tumor size			< 0.001
<4cm	1(reference)		
4-7cm	5.21	2.96-9.18	

OR, Odds ratio; 95% CI, 95% Confidence interval.

RESULTS

Patients' demographics and pathological characteristics

Of 1,376 cT1 RCC patients, 75 patients (5.5%) were noted with postoperative upstaging to pT3a, and 73 patients had detailed postoperative pathological information. Overall, thirty-nine (53.4%) patients were found to have PF invasion, 8 (11.0%) with SF invasion, 1 with collecting system invasion, 21 (28.8%) with renal or segmental RV invasion, and 4 (0.05%) with both RF and RV invasion.

The clinical and pathological features of RCC patients by upstaging status are shown in Table 1. Patients upstaging to pT3a were older (63.08 vs. 57.34 years, $P < .001$), with larger tumor size (5.24 vs. 3.95cm, $P < .001$) and higher Fuhrman grade (37.3% vs. 7.5%, $P < .001$). Clinical symptoms including hematuria, abdominal pain and abdominal palpable mass were more common in patients upstaging to pT3a (46.7% vs. 25.2%, $P < .001$). For imaging features, tumor necrosis (40% vs. 19.9%, $P < .001$), irregular tumor edge (73.3% vs. 59.0%, $P < .001$) and closer to the collecting system or sinus were more likely to result in upstaging to pT3a. Patients upstaged to pT3a were more likely to have undergone RN (92.1% vs. 70%, $P < .001$) as compared with non-upstaged patients. Among the three clinical symptoms, the most common one was abdominal pain which accounts for 14.7% and 26.7% of all non-upstaging and upstaging patients. Patients with abdominal pain ($P = .006$) and abdominal masses ($P < .001$) differed in non-upstaging and upstaging groups with statistical significance.

Analysis of predictors for upstaging and RFS

Univariate and multivariate logistic regression were performed to identify the independent predictors of upstaging, with the results shown in Table 2. The Fuhrman grade (OR = 5.37; 95% CI: 3.05-9.47, $P < .001$), clinical symptom (OR = 2.19, 95% CI: 1.31-3.68, $P = .003$), tumor size (OR = 2.97; 95% CI: 1.60-5.51, $P = .001$), age (OR = 1.05; 95% CI: 1.02-1.07, $P = .001$), tumor necrosis (OR=2.76; 95% CI: 1.62-4.72, $P = .001$) and tumor edge irregularity (OR = 2.55; 95% CI: 1.44-4.52, $P = .002$) were independent predictors of upstaging.

The differences of RFS between different clinical and

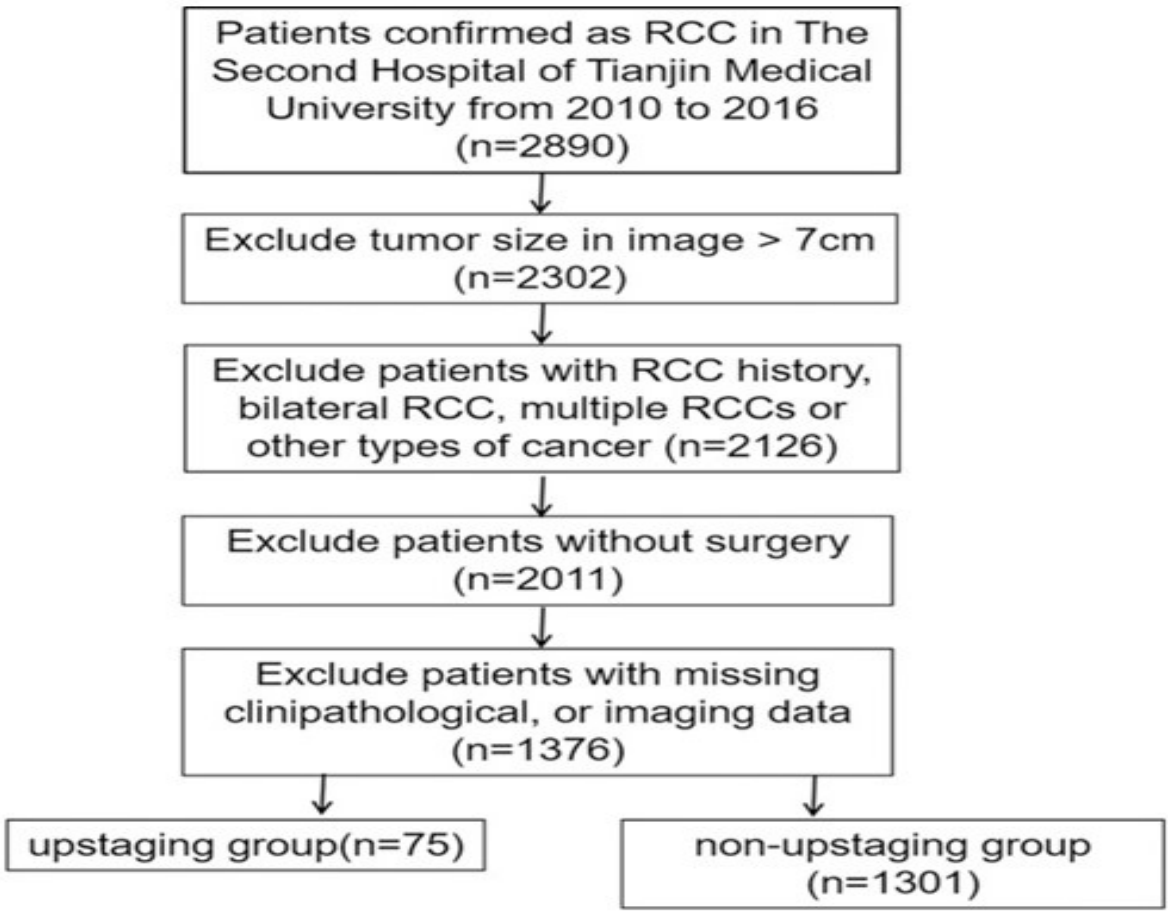

Figure 2. Flow diagram of the clinical T1 renal cell carcinoma patients included in the study.

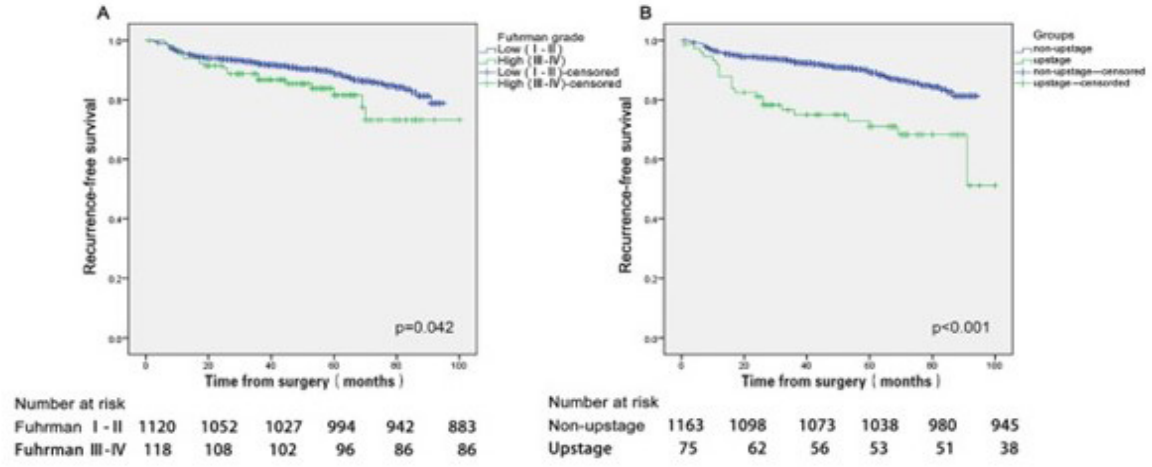

Figure 3. Comparison of recurrence free survival of clinical T1 renal cell carcinoma patients between **(A)** Fuhrman I-II and Fuhrman III-IV; **(B)** upstaging and non-upstaging to pT3a.

pathological characteristics were also compared with Kaplan-Meier method and log-rank test (Supplementary Figure 1). The result showed that only Fuhrman nuclear grade (log-rank, $p = 0.045$) and upstaging (log-rank, $p < 0.001$) were significantly related to the RFS of cT1 RCC patients (Figure 3A, B). The 5-year RFS probabilities were 73.3% and 91.1% for upstaging and non-upstaging to pT3a RCC patients. The result of univariate and multivariate Cox regression showed that only postoperative upstaging was an independent predictor of RFS for cT1 RCC patients (HR = 2.55; 95% CI: 1.58-4.12, $P < .001$) (**Table 3**).

A total of 1,238 patients (90.0%) were followed up and were included in the survival analysis. The median (IQR) follow-up duration was 51 (35-69) months, during which local recurrence and distant metastasis were observed in 6 (8%) and 16 (21.3%) patients in pT3a group. In contrast, 56 (4.8%) and 86 (7.4%) patients without upstaging were noted with local recurrence and distant metastasis respectively. Tumor progression of 1,238 patients was shown in **Table 4**.

Construction and validation of nomogram model

Nomogram model (**Figure 4A**) for predicting upstaging to pT3a was constructed based on the result of univariate and multivariate logistic regression. The ROC curve was plotted based on the nomogram model, with the C-index of the nomogram of 0.842 (**Figure 4B**). Bootstrap self-sampling method and calibration curves were employed to validate the nomogram model. A 1000 time self-sampling was adopted for the calibration

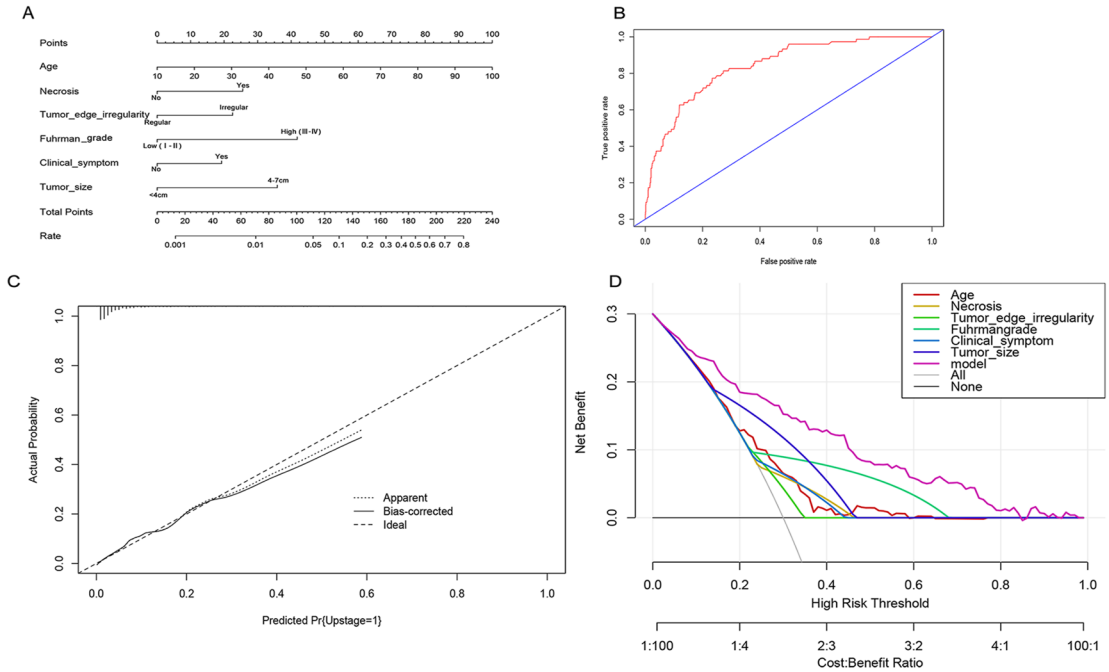

Figure 4. (A) Nomogram model of cT1 renal cell carcinoma upstaging to pT3a. **(B)** ROC curve of the nomogram model for upstaging. **(C)** Calibration curve of the nomogram model for upstaging. **(D)** Decision curve analysis of the nomogram model for upstaging.

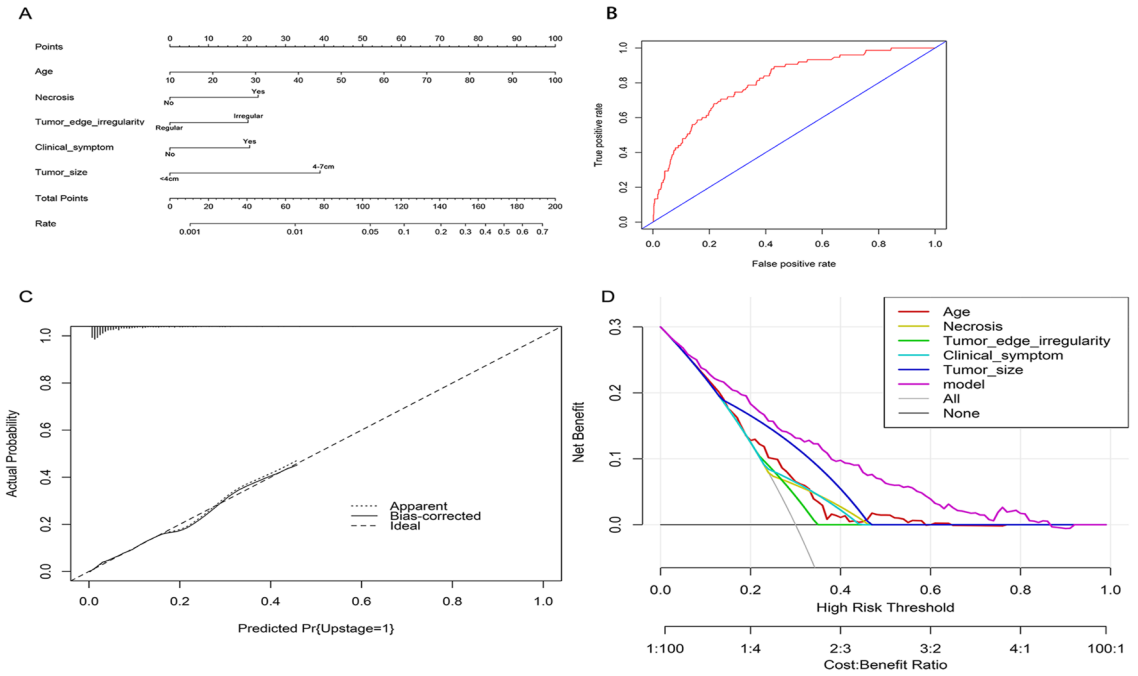

Figure 5. (A) Nomogram model of preoperative patameters for cT1 renal cell carcinoma upstaging to pT3a. **(B)** ROC curve of the nomogram model of preoperative parameters for upstaging. **(C)** Calibration curve of the nomogram model of preoperative parameters for upstaging. **(D)** Decision curve analysis of the nomogram model of preoperative parameters for upstaging.

curve, and it was be proven that the calibration curve fits well with the ideal curve (**Figure 4C**). The result of decision clinical analysis (**Figure 4D**) also showed that the clinical applicability of the nomogram model was better than that of single factors. Considering Fuhrman grade is an postoperative parameter for most patients not undergoing renal biopsy before surgery, the logistic regression and nomogram plotting were also performed (**Figure 5A**) with the other 5 preoperative parameters, which showed statistical significance(**Table 5**). The ROC curve, calibration curve and decision curve analysis were also performed, and the C-index of the nomogram model with preoperative parameters was 0.806 (**Figure 5B-D**).

DISCUSSION

Based on the TNM staging system, pT3a RCC includes tumor extending into renal or renal segmental vein, PF or SF, collecting system but not beyond Gerota's fascia [(1)]. At present, clinical diagnosis and staging of RCC mainly relies on non-enhanced CT combined with contrast-enhanced CT with higher accuracy. It is generally believed that blurred margin of peritumoral fat and irregular tumor nodules infiltrating peritumoral fat indicate PF infiltration for exophytic RCC according to the images. While the irregular margin, unclear boundary of SF or PF and tumor necrosis may imply the possibility of T3a for endophytic RCC[(3)]. Previous studies have indicated that the incidence of upstaging to pT3a was from 4.8% to 31% [(4,9)], while the incidence of upstaging was 5.5% in our current study.

The result of our study suggested that age was associated with upstaging, which confirmed the result of the previous study that the risk of upstaging in RCC increased in older patients[(10)]. Moreover, clinical symptom was an independent predictor of upstaging and the proportion of symptomatic patients in the upstaging group were significantly higher[(11)]. As the classic triad of flank pain, palpable abdominal mass and visible haematuria is rare (6–10%) and correlates to advanced disease and aggressive histology in RCC, attention should be taken to the risk of upstaging when clinical symptoms occur in RCC patients.

The proportion of irregular tumor edge was higher in the upstaging group as an independent predictor, and some studies suggested that the biopsy at irregular tumor edge could confirm the pathological stage during surgery[(12-13)]. One of our previous studies reported that there was statistical significance of overall survival (OS) and cancer-specific survival (CSS) in different tumor growth patterns for RCC patients, including single nodule pattern, multinodule fusion pattern and infiltration pattern . After the comparison of the image characteristics in different tumor growth patterns, it was found that tumor margin for RCC patients with infiltrative growth pattern seemed to be more irregular [(14)]. As a consequence, tumour edge irregularity was defined in details and the relationship was examined between it and upstaging. Our study has confirmed tumor edge irregularity as an independent predictor of upstaging. Collins and Chen et al. found that tumor necrosis in pathology was an independent prognostic factor for RCC patients and had higher probability to infiltrate collecting system, resulting in poor prognosis[(15-16)]. SOKHI et al. reported that tumor necrosis in CT, irregular tumor edge and direct contact between tumor and PF or SF could increase the probability of local invasion[(3)]. Our study found that tumor necrosis in imaging was an independent predictor for upstaging. Previous studies have shown that tumor size was an im-

portant predictor of prognosis for pT3a RCC patients and upstaging, which is consistent with the result of our study. All-cause mortality increased by about 8% and cancer specific survival (CSS) decreased by about 14% for each 1cm increased in tumor size[17-18]. Many studies have shown that Fuhrman grade was closely related to upstaging for RCC patients, and higher Fuhrman grade reflected higher tumor invasiveness [6,11]. Three hundred and ninety (30%) non-upstaging RCC patients received NSS, with the positive surgical margin (PSM) rate of 1.4%. Only 6 (7.9%) patients upstaging to pT3a RCC patients received NSS and no PSM was found. Several studies reported that PSM was an independent predictor of upstaging, closely related to poor prognosis[19-21]. As PSM rate can not be statistically analyzed in our study, it was not included in the nomogram model.

The result of our study showed that patients receiving RN had a higher probability of upstaging , but the type of nephrectomy was not an independent predictor of upstaging. CT1 RCC patients who underwent RN were more likely to be detected with PF and SF invasion than NSS, leading to a higher probability of upstaging to pT3a. Furthermore, this association may be the result of selection bias, since patients with tumors of more"aggressive" features were more likely to undergo RN. Many studies reported the correlation between RENAL scores and upstaging, Fuhrman nuclear grade and prognosis. When comparing the relationship between variables in RENAL scores and upstaging, tumor size and renal mass's hilar location seem to be more important . However, only tumor size is an independent predictor of upstaging after multivariate logistic regression in our study.

The previous study suggested that cT1 RCC patients upstaging to pT3a might increase the risk of local recurrence and be associated with poor prognosis[22-23]. Lee et al. indicated that patients with cT1 upstaging to pT3 had poorer RFS, CSS and OS as compared with non-upstaging patients(10). Lai et al. compared the differences of oncological outcomes between 55 cT1 RCC patients upstaging to pT3a and 374 pT1 non-upstaging RCC patients, and the result showed that upstaging patients had low OS and high recurrence rates[24]. However, some studies also reported no difference of prognosis between upstaging and non-upstaging RCC patients[9]. It was found in our study that upstaging was an independent prognostic factor of RFS for cT1 RCC patients. Previous study has developed a nomogram model based on multiple preoperative blood indexes and oncological characteristics with the C-index of 0.756 and 0.712 in the training and validation cohorts. Age, the ratio of the tumor maximum and minimum diameter, fibrinogen and tumor size were included in the nomogram model[25]. The C-index of our nomograms are 0.842 and 0.806, which is higher than the existing nomogram. We also performed calibration curve and decision curve analysis. Furthermore, our study firstly defined the 'tumor edge irregularity' in detail on the basis of our previous study.and found that it is an independent predictor of upstaging. Physicians could use nomogram plots to predict the patients' risk of upstaging and prognosis accurately and could also treat patients with higher risk by more aggressive approaches, including removing more peritumoral fat during surgery, performing RN rather than NSS, shortening the follow-up interval, etc.

There are still limitations in our study. Firstly, this is a single-center retrospective study, and multi-center and prospective studies are required to validate the model in the future. Secondly, the large difference of sample size between the two groups in our study may reduce the statistical efficiency, yet not affect the result of the statistical inference. Thirdly, the follow-up management of RCC patients is not standardized and the duration of follow-up needs to be extended to minimize the missing data.

CONCLUSIONS

In conclusion, the rate of cT1 upstaging to pT3a for RCC patients can not be negligible (5.5%), and postoperative upstaging was an independent predictor of RFS. Age, clinical symptom, tumor size, Fuhrman grade, tumor necrosis in CT and tumor edge regularity were independent predictors for upstaging and two nomogram models were built based on them with excellent discrimination and better clinical application. RN should routinely remove all PF, which may contribute to the diagnosis of pathological staging and may reduce the risk of tumor residual or local recurrence.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

APPENDIX

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