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Prognostic Significance of Grade Discrepancy Between Primary Tumor and Venous Thrombus in Nonmetastatic Clear-cell Renal Cell Carcinoma: Analysis of the REMEMBER Registry and Implications for Adjuvant Therapy

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Abstract

Background: Further stratification of the risk of recurrence of clear-cell renal cell carcinoma (ccRCC) with venous tumor thrombus (VTT) will facilitate selection of candidates for adjuvant therapy.

Objective: To assess the impact of tumor grade discrepancy (GD) between the primary tumor (PT) and VTT in nonmetastatic ccRCC on disease-free survival (DFS), overall survival (OS), and cancer-specific survival (CSS).

Design, setting, and participants: This was a retrospective analysis of a multi-institutional nationwide data set for patients with pT3N0M0 ccRCC who underwent radical nephrectomy and thrombectomy.

Outcomes measurements and statistical analysis: Pathology slides were centrally reviewed. GD, a bidirectional variable (upgrading or downgrading), was numerically defined as the VTT grade minus the PT grade. Multivariable models were built to predict DFS, OS, and CSS.

Results and limitations: We analyzed data for 604 patients with median follow-up of 42 mo (excluding events). Tumor GD between VTT and PT was observed for 47% (285/604) of the patients and was an independent risk factor with incremental value in predicting the outcomes of interest (all $p < 0.05$). Incorporation of tumor GD significantly improved the performance of the ECOG-ACRIN 2805 (ASSURE) model. A GD-based model (PT grade, GD, pT stage, PT sarcomatoid features, fat invasion, and VTT consistency) had a c index of 0.72 for DFS. The hazard ratios were 8.0 for GD = +2 ($p < 0.001$), 1.9 for GD = +1 ($p < 0.001$), 0.57 for GD = −1 ($p = 0.001$), and 0.22 for GD = −2 ($p = 0.003$) versus GD = 0 as the reference. According to model-converted risk scores, DFS, OS, and CSS significantly differed between subgroups with low, intermediate, and high risk (all $p < 0.001$).

Conclusions: Routine reporting of VTT upgrading or downgrading in relation to the PT and use of our GD-based nomograms can facilitate more informed treatment decisions by tailoring strategies to an individual patient's risk of progression.

Patient summary: We developed a tool to improve patient counseling and guide decision-making on other therapies in addition to surgery for patients with the clear-cell type of kidney cancer and tumor invasion of a vein.

1. Introduction

The KEYNOTE-564 study opened the door to the use of adjuvant immune checkpoint inhibitors (ICIs) for locally advanced clear-cell renal cell carcinoma (ccRCC) [1,2]. Specifically, patients with concomitant venous tumor thrombus (VTT) have a higher risk of relapse and could be ideal candidates for this emerging adjuvant treatment. However, conflicting results from other adjuvant trials investigating different ICI-based regimens [3] and the lack of biomarkers for aiding proper candidate selection limit the strength of the latest recommendations from the European Association of Urology guidelines on the use of adjuvant therapy [4]. It could be argued that the cost/benefit ratio for adjuvant immunotherapy would be more favorable for patients at higher risk of recurrence. Indeed, a recent study using a decision analytic Markov model found that pembrolizumab is cost effective only for the subset of patients with ccRCC with the highest 5-yr risk of progression after surgery [5]. However, ccRCC with VTT is a heterogeneous disease, with 5-yr disease-free survival (DFS) prognosis ranging from 33% to 83% according to estimates from the ECOG-ACRIN 2805 (ASSURE) prognostic model [6,7].

Several prognostic models, including ASSURE, have been proposed for predicting outcomes after surgery with curative intent in the overall population with nonmetastatic RCC [7–16]. The lack of VTT characteristics in these models may limit their ability to assess individualized risk for the subset of patients with VTT. Additional large-scale studies have focused on the prognostic value of typical clinicopathologic factors and thrombus-related features, but results are inconsistent and controversy regarding the role of tumor grade remains [17–21]. In current clinical practice, tumor grade is assigned according to the highest-grade area observed within the primary tumor (PT), while that in the VTT is ignored. Investigators recently provided evidence of phenotypic heterogeneity between the PT and VTT via single-cell RNA sequencing analysis [22]. Moreover, the VTT grade relative to the PT grade may be a critical predictor of metastatic potential [23].

The incidence and prognostic impact of tumor grade discrepancy (GD; upgrading or downgrading) between a VTT and PT have not been clarified. Our aim was to use this unique characteristic of ccRCC with VTT to further stratify the prognosis for these patients. We conducted centralized review of pathology slides for a large multi-institutional data set to identify latent "very high-risk" disease in patients who might potentially benefit the most from adjuvant ICI therapy.

2. Patients and methods

2.1. Study population and variables

The REMEMBER (Research of Multi-institution in East-China on Malignant and Benign Epithelial Renal Tumors) VTT project retrospectively collected data for consecutive patients who underwent radical nephrectomy and thrombectomy for cT3N0M0 RCC (American Joint Committee on Cancer [AJCC] 2017 TNM scheme) between 2012 and 2021 in 19 high-volume tertiary centers in China. Institutional review board approval (2021NZKY-004-01) was obtained before data collection. Deidentified information was provided by each center and compiled within an encrypted database by a single investigator (L.Q.) who was blinded to the study design. Data for 1302 patients were identified by querying the REMEMBER database using the following inclusion criteria, which mirror the eligibility criteria for the intermediate- to high-risk subset in the KEYNOTE-564 trial (accounting for 86.5% of the participants enrolled; group prone to overtreatment) [1,24]: (1) pT3N0 disease with ccRCC histology; (2) pathology confirmation of venous tumor extension with a negative resection margin; and (3) no neoadjuvant therapy or history of other malignancy. We excluded 698 patients (54%) because of missing preoperative abdominal cross-sectional computed tomography or magnetic resonance images for review (n = 316), missing values for candidate predictive variables (n = 225), missing follow-up information (n = 124), or missing pathology slides for centralized review (n = 19), or mortality within 30 d after surgery (n = 14).

Data for the following pathologic characteristics were collected: ccRCC type according to the 2022 World Health Organization (WHO) classification [25], presence of tumor necrosis, sarcomatoid or rhabdoid differentiation, WHO/International Society of Urological Pathology (ISUP) grade [26] for both the PT and the VTT specimen, thrombus consistency (solid vs friable) [21], vascular wall invasion [27], pathologic T stage according to the 8th edition of the TNM classification [28,29], and renal sinus and/or perinephric fat invasion. Additional clinical data of interest are provided in the Supplementary material. All pathology slides were centrally reviewed by two independent senior genitourinary pathologists (H.C. and Q.R.). Discrepancies or heterogeneous VTTs were adjudicated by a third senior uro-oncologic pathologist (X.Z.) and resolved via consensus.

2.2. Statistical analysis

2.2.1. Measurement of tumor grade and definition of GD

In current routine clinical practice, overall tumor grade is based on the highest-grade area observed within the PT. Applying the same principle, we conducted four measurements: (1) grade within the PT alone (PT grade); (2) grade within the VTT alone (VTT grade); (3) the single highest grade for the PT and VTT together (PT-VTT grade); and (4) GD, defined as the VTT grade minus the PT grade, as a bidirectional variable (upgrading or downgrading) numerically recorded as −2, −1, 0, 1, or 2.

Sankey diagrams were used to show the relationship between PT grade and VTT grade.

2.2.2. Incremental value of GD in predicting outcomes and construction of a GD-based model

Considering the aim of this study and the number of events for DFS, overall survival (OS), and cancer-specific survival (CSS). Kaplan-Meier method was used to estimate survival curves and log-rank test for trend was used to detect ordered differences in survival curves by GD value. Univariable and multivariable Cox regression analyses were used to test the association between parameters and outcomes,

reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Model development for predicting DFS, OS and CSS was performed according to the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guideline [30] and the methodologic criteria established by the AJCC Precision Medicine Core [31]. To evaluate the incremental predictive value of GD, three tumor grade measures (PT grade, PT-VTT grade, PT grade plus GD) were separately incorporated for model development. Correlated Harrell's c-index values were compared with right-censored survival outcomes via the one-shot nonparametric approach [32]. Additional methodology for model development, evaluation, and sensitivity analysis is described in the Supplementary material.

3. Results

3.1. Patient characteristics and association of GD with survival

A total of 604 patients were included in the analysis. Baseline characteristics were comparable between the excluded and included groups, except for the presence of hypertension and the proportion of right-sided PTs (Supplementary Table 1). A total of 4651 slides were reviewed by pathologists to assess tumor grading. The concordance between two independent investigators was 99%; five cases with a small amount of pleomorphic nuclei or giant tumor cells but without rhabdoid or sarcomatoid features were adjudicated by a third senior pathologist. Of the patients included in the final analysis, 64% were male and 54% had a primary lesion in the right kidney with a median tumor size of 7.8 cm. The VTT level (Mayo classification) was 0 in 49% of patients, I in 21%, II in 17%, III in 9.4%, and IV in 24.3%. Some 27% (164 cases) received adjuvant systemic antiangiogenic therapy. No patient received adjuvant ICI therapy.

Over median follow-up of 42 mo (interquartile range [IQR] 21–67), calculated excluding events, the median DFS, OS, and CSS were 60 mo (IQR 24–not reached [NR]), 76 mo (IQR 33–NR), and 87 mo (IQR 35–NR), respectively. The probability of 5-yr DFS, 5-yr OS, and 5-yr CSS for the entire cohort was 0.48, 0.59, and 0.62, respectively (Supplementary Table 2).

Pathologic characteristics, including comprehensive VTT evaluation in terms of tumor grade, necrosis, sarcomatoid and rhabdoid differentiation, and tumor consistency, are listed in Table 1. ISUP grade for the PT was G1 in 0.3%, G2 in 24%, G3 in 54%, and G4 in 23% of patients. The GD was 0 (VTT grade = PT grade) in 319 patients (53%), 2 (VTT upgrading by 2 classes) in 11 (1.8%), 1 (upgrading by 1 class) in 119 (20%), −1 (downgrading by 1 class) in 137 (23%), and −2 (downgrading by 2 classes) in 18 (3%). The discrepancy between PT grade and VTT grade is visualized in Sankey diagrams in Figure 1A–C. Log-rank tests for trend revealed negative correlations between GD and DFS, OS, and CSS probability in the separate PT grade groups (Fig. 1D–F for DFS, and Supplementary Fig. 1 for OS and CSS). The grade association between PT and VTT and the ordered difference of GD for DFS, OS, and CSS by pT stage are shown in Figure 2 and Supplementary Figure 2.

Table 1 – Clinical and pathologic characteristics (n = 604)

Variable	
Asian ethnicity/race, *n* (%)	604 (100)
Median age at diagnosis, yr (IQR)	61 (53–68)
Male, *n* (%)	387 (64)
Median body mass index, kg/m^2 (IQR)	23.4 (21.7–26)
Gross hematuria, *n* (%)	203 (34)
Hypertension, *n* (%)	191 (32)
Diabetes, *n* (%)	100 (17)
Chronic kidney disease, *n* (%)	131 (22)
Median serum albumin, g/l (IQR)	38 (33.9–41)
Median serum hemoglobin, g/l (IQR)	115 (98–132)
Median serum alkaline phosphatase, U/l (IQR)	85 (67–117)
Median serum lactate dehydrogenase, U/l (IQR)	186 (154–237)
Median NLR (IQR)	3.5 (2.3–6.1)
Right-sided tumor side, *n* (%)	328 (54)
Median clinical tumor size, cm (IQR)	7.8 (5.8–9.9)
Mayo thrombus level, *n* (%)	
0	295 (48.8)
I	126 (20.9)
II	100 (16.6)
III	57 (9.4)
IV	26 (4.3)
Minimally invasive surgical approach, *n* (%)	280 (46)
Median operative time, h (IQR)	4.3 (3.4–5.7)
Perioperative transfusion, *n* (%)	295 (49)
Median length of stay, d (IQR)	14 (10–18)
Antiangiogenic adjuvant systemic therapy, *n* (%)	164 (27)
Pathologic stage, *n* (%)	
pT3a	295 (49)
pT3b	145 (24)
pT3c	164 (27)
PT grade, *n* (%)	
I	2 (0.3)
II	143 (23.7)
III	323 (53.5)
IV	136 (22.5)
PT-VTT grade, *n* (%)	
I	2 (0.3)
II	87 (14.4)
III	294 (48.7)
IV	221 (36.6)
Grade discrepancy, *n* (%)	
0 (VTT grade equals PT grade)	319 (52.8)
1 (VTT upgrading by 1 class)	119 (19.7)
2 (VTT upgrading by 2 classes)	11 (1.8)
−1 (VTT downgrading by 1 class)	137 (22.7)
−2 (VTT downgrading by 2 classes)	18 (3)
PT necrosis, *n* (%)	321 (53)
PT sarcomatoid, *n* (%)	94 (16)
PT rhabdoid, *n* (%)	68 (11)
VTT necrosis, *n* (%)	191 (32)
VTT sarcomatoid, *n* (%)	57 (9.4)
VTT rhabdoid, *n* (%)	43 (7.1)
Solid thrombus consistency, *n* (%)	337 (56)
Vascular wall invasion, *n* (%)	268 (44)
Fat invasion, *n* (%)	176 (29)

IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; PT = primary tumor; VTT = venous tumor thrombus.

3.2. Independent and incremental value of GD in predicting outcomes

On univariable analysis, preoperative hemoglobin, clinical tumor size, operative time, perioperative transfusion, pathologic stage, PT grade, PT-VTT grade, GD, PT sarcomatoid features, PT rhabdoid features, VTT sarcomatoid features, VTT rhabdoid features, VTT friable consistency, vascular wall invasion, and fat invasion were associated with higher risk of DFS, OS, and CSS (all $p < 0.05$; Table 2). GD was an independent risk factor in predicting outcomes and its incremental indices were statistically significant in predicting DFS, OS, and CSS (Supplementary Table 3). Additional results are presented in the Supplementary material.

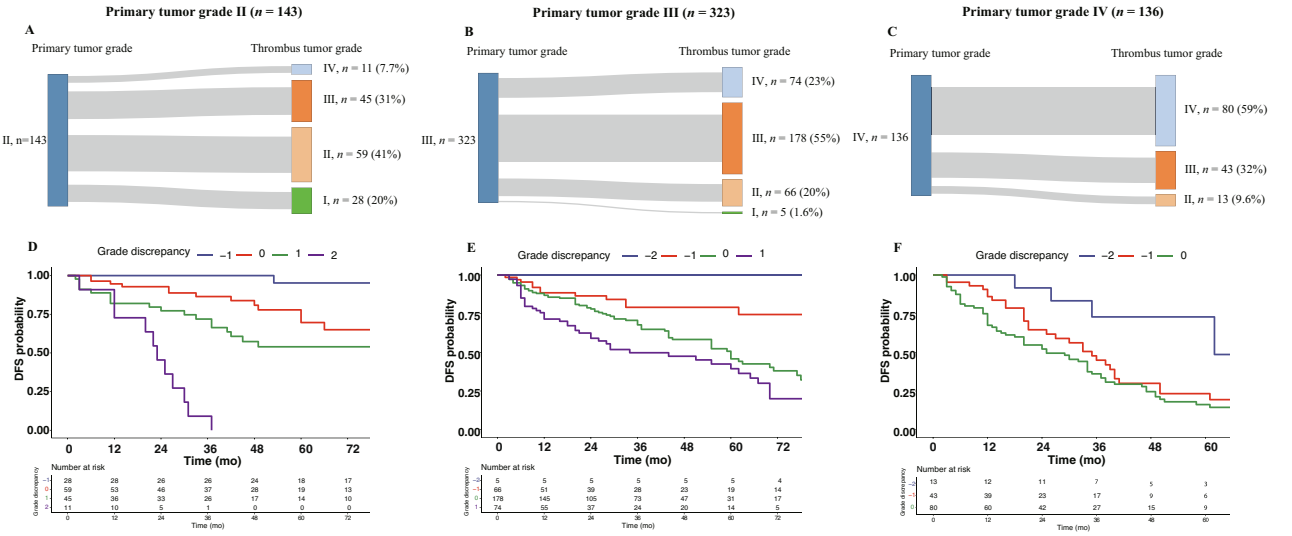

Fig. 1 – (A–C) Sankey diagrams showing the relationship between primary tumor grade and venous tumor thrombus grade and (D–F) Kaplan-Meier survival curves for grade discrepancy rankings with log-rank tests for ordered differences in disease-free survival (DFS) according to the primary tumor grade. Grade discrepancy for primary tumors of (A) grade II, (B) grade III, and (C) grade IV. DFS curves for ordered grade discrepancy (tumor thrombus grade minus the primary tumor grade) for primary tumors of (D) grade II, (E) grade III, and (F) grade IV. There were two cases of grade I primary tumor without upgrading for the venous tumor thrombus, and this class is not shown here.

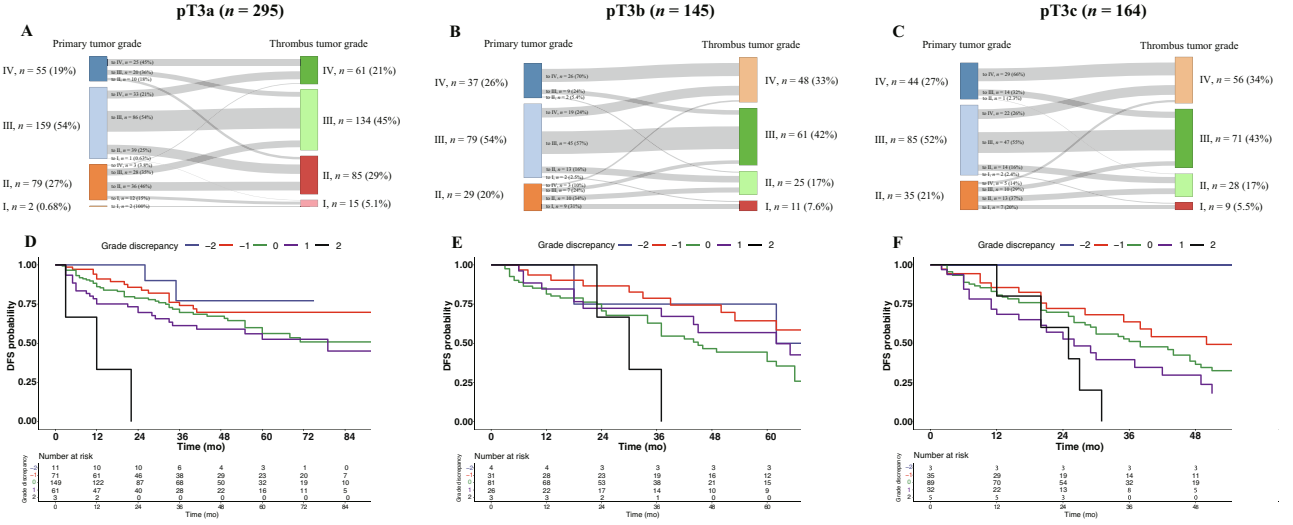

Fig. 2 – (A–C) Sankey diagrams showing the relationship between primary tumor grade and venous tumor thrombus grade and (D–F) Kaplan-Meier survival curves for grade discrepancy rankings with log-rank tests for ordered differences in disease-free survival (DFS) according to the pT stage. Grade discrepancy (tumor thrombus grade minus the primary tumor grade) in (A) stage pT3a, (B) stage pT3b, and (C) stage pT3c. DFS curves for ordered grade discrepancy in (D) stage pT3a, (E) stage pT3b, and (F) stage pT3c.

Incorporation of GD in the ASSURE model improved the c index from 0.58 (95% CI 0.55–0.62) to 0.63 (95% CI 0.6–0.67) for DFS prediction ($p < 0.001$) and from 0.6 (95% CI 0.56–0.63) to 0.63 (95% CI 0.6–0.67) for OS prediction ($p = 0.014$; Supplementary Table 4).

Using least absolute shrinkage and selection operator (LASSO) Cox regressions, final GD-based models for predicting DFS, OS and CSS probability were built and presented as nomograms (Fig. 3A–C). Six variables (PT grade and GD, pT stage, PT sarcomatoid differentiation, VTT consistency, and fat invasion) were included as independent factors for prediction of DFS; five factors (PT grade, GD, pT stage, PT sarcomatoid differentiation, and fat invasion) were included for prediction of OS and CSS. Risk formulas according to the estimated Cox regression coefficients used in the nomograms (Table 3) are provided in the Supplementary material. Sensitivity analysis in the subgroup of patients who did not receive adjuvant therapy confirmed the independent prognostic capability of GD (Supplementary Table 5).

The nomograms and risk scores had c-index values of 0.72 for DFS, 0.74 for OS, and 0.74 for CSS, with corresponding corrected c-index values of 0.72, 0.74, and 0.74 on internal validation via bootstrap resampling. The small correction for the c index (<1%) indicates a low risk of overfitting. The area under the receiver operating characteristic curve for the nomogram was 0.78, 0.8, and 0.81 for predicting 5-yr DFS, OS, and CSS, respectively (Supplementary Fig. 3). The calibration curves showed concordance between

Table 2 – Univariable Cox regression estimates for the three survival endpoints (n = 604)

Risk factor	Disease-free survival		Overall survival		Cancer-specific survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at diagnosis (continuous)	1.00 (0.99–1.01)	0.9	1.00 (0.99–1.01)	0.6	1.00 (0.99–1.01)	0.9
Female sex (vs male)	1.23 (0.97–1.56)	0.085	1.32 (1.01–1.73)	**0.044**	1.30 (0.98–1.73)	0.067
Body mass index (continuous)	0.99 (0.95–1.03)	0.5	0.98 (0.94–1.03)	0.5	0.99 (0.95–1.04)	0.8
Gross hematuria (yes vs no)	1.04 (0.81–1.33)	0.7	1.06 (0.80–1.40)	0.7	1.08 (0.80–1.44)	0.6
Hypertension (yes vs no)	0.86 (0.66–1.12)	0.3	0.97 (0.72–1.30)	0.8	0.96 (0.71–1.31)	0.8
Diabetes (yes vs no)	1.20 (0.88–1.62)	0.2	1.51 (1.09–2.10)	**0.013**	1.61 (1.15–2.26)	**0.005**
Preoperative CKD (yes vs no)	1.01 (0.76–1.34)	0.9	1.16 (0.85–1.59)	0.4	1.06 (0.75–1.48)	0.8
Serum albumin (continuous)	0.98 (0.96–1.01)	0.16	0.98 (0.95–1.00)	0.096	0.98 (0.95–1.00)	0.066
Hemoglobin (continuous)	0.99 (0.99–1.00)	**<0.001**	0.99 (0.98–1.00)	**0.002**	0.99 (0.98–1.00)	**0.002**
Serum ALP (continuous)	1.00 (1.00–1.00)	0.12	1.00 (1.00–1.00)	0.19	1.00 (1.00–1.00)	0.19
Serum LDH (continuous)	1.00 (1.00–1.00)	0.21	1.00 (1.00–1.00)	0.077	1.00 (1.00–1.00)	**0.027**
NLR (continuous)	1.03 (0.99–1.07)	0.14	1.05 (1.00–1.10)	**0.031**	1.03 (0.99–1.08)	0.15
Tumor side (right vs left)	0.76 (0.60–0.96)	**0.02**	0.79 (0.61–1.04)	0.092	0.76 (0.57–1.00)	0.053
Clinical tumor size (continuous)	1.04 (1.00–1.08)	**0.031**	1.05 (1.00–1.10)	**0.015**	1.05 (1.01–1.10)	**0.018**
Surgical approach (MIS vs open)	0.80 (0.63–1.02)	0.067	0.95 (0.72–1.24)	0.7	0.92 (0.69–1.22)	0.6
Operative time (continuous)	1.08 (1.01–1.15)	**0.017**	1.10 (1.03–1.18)	**0.006**	1.12 (1.04–1.20)	**0.002**
Perioperative transfusion (yes vs no)	1.84 (1.45–2.34)	**<0.001**	1.88 (1.43–2.48)	**<0.001**	1.85 (1.39–2.47)	**<0.001**
Length of stay (continuous)	1.01 (0.99–1.02)	0.16	1.02 (1.00–1.03)	**0.016**	1.02 (1.00–1.03)	**0.039**
Adjuvant systemic therapy (yes vs no)	1.41 (1.10–1.82)	**0.006**	1.36 (1.02–1.81)	**0.035**	1.21 (0.89–1.65)	0.2
Pathologic stage (vs pT3a)						
pT3b	1.65 (1.23–2.21)	**<0.001**	1.79 (1.27–2.52)	**<0.001**	1.75 (1.22–2.52)	**0.002**
pT3c	2.28 (1.73–3.01)	**<0.001**	2.69 (1.95–3.70)	**<0.001**	2.69 (1.92–3.75)	**<0.001**
PT grade (vs I–II)						
III	1.75 (1.25–2.45)	**0.001**	1.70 (1.15–2.51)	**0.007**	1.63 (1.09–2.44)	**0.017**
IV	4.04 (2.84–5.74)	**<0.001**	3.88 (2.61–5.77)	**<0.001**	3.66 (2.42–5.52)	**<0.001**
PT-VTT grade (vs I–II)						
III	3.12 (1.81–5.36)	**<0.001**	3.34 (1.72–6.46)	**<0.001**	3.47 (1.73–6.95)	**<0.001**
IV	8.24 (4.83–14.04)	**<0.001**	8.95 (4.69–17.09)	**<0.001**	8.83 (4.46–17.46)	**<0.001**
Grade discrepancy (vs 0)						
1 (VTT upgrading by 1 class)	1.08 (0.81–1.45)	0.6	1.02 (0.73–1.43)	0.9	1.04 (0.73–1.47)	0.8
2 (VTT upgrading by 2 classes)	3.29 (1.77–6.09)	**<0.001**	3.94 (2.11–7.35)	**<0.001**	3.81 (1.98–7.33)	**<0.001**
−1 (VTT downgrading by 1 class)	0.53 (0.38–0.74)	**<0.001**	0.55 (0.37–0.80)	**0.002**	0.52 (0.34–0.78)	**0.002**
−2 (VTT downgrading by 2 classes)	0.28 (0.10–0.76)	**0.012**	0.28 (0.09–0.88)	**0.03**	0.42 (0.15–1.14)	0.088
PT necrosis (yes vs no)	1.15 (0.91–1.45)	0.3	1.13 (0.86–1.47)	0.4	1.15 (0.87–1.53)	0.3
PT sarcomatoid (yes vs no)	3.49 (2.71–4.49)	**<0.001**	3.97 (3.00–5.25)	**<0.001**	3.70 (2.75–4.98)	**<0.001**
PT rhabdoid (yes vs no)	2.45 (1.82–3.28)	**<0.001**	1.99 (1.39–2.86)	**<0.001**	1.99 (1.39–2.86)	**<0.001**
VTT necrosis (yes vs no)	1.06 (0.83–1.37)	0.6	0.92 (0.67–1.25)	0.6	0.92 (0.67–1.25)	0.6
VTT sarcomatoid (yes vs no)	3.43 (2.54–4.64)	**<0.001**	3.52 (2.49–4.98)	**<0.001**	3.52 (2.49–4.98)	**<0.001**
VTT rhabdoid, yes vs no	3.46 (2.49–4.81)	**<0.001**	3.67 (2.53–5.30)	**<0.001**	3.67 (2.53–5.30)	**<0.001**
Thrombus consistency (friable vs solid)	1.78 (1.41–2.25)	**<0.001**	1.69 (1.27–2.24)	**<0.001**	1.69 (1.27–2.24)	**<0.001**
Vascular wall invasion (yes vs no)	1.42 (1.12–1.79)	**0.003**	1.52 (1.15–2.01)	**0.003**	1.52 (1.15–2.01)	**0.003**
Fat invasion (yes vs no)	1.84 (1.45–2.33)	**<0.001**	2.29 (1.73–3.03)	**<0.001**	2.29 (1.73–3.03)	**<0.001**

CKD = chronic kidney disease; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio; MIS = minimally invasive surgery; PT = primary tumor; VTT = venous tumor thrombus; HR = hazard ratio; CI = confidence interval.

the predicted survival probability and the actual survival observed at 3, 5, and 7 yr (Fig. 3D–F).

3.3. *Clinical utility*

Decision curve analyses for the nomograms are presented in Figure 3G–I. Our nomograms provided consistent positive and larger net benefit across a broad range of risk thresholds (10–80%) in comparison to the two default strategies and the ASSURE model.

Optimal cutoff values for the risk score according to the X-tile method for division into three risk groups were 0.87 and 1.9 for DFS, 1.0 and 1.9 for CSS, and 0.98 and 2.2 for OS. Patients in higher risk groups had worse survival outcomes than those in lower risk groups (Fig. 4). In the low-, intermediate-, and high-risk subgroups, 5-yr DFS probability was 0.8, 0.41, and 0.13, 5-yr OS probability was 0.87, 0.49, and 0.18, and 5-yr CSS probability was 0.87, 0.53, and 0.22, respectively (all $p < 0.001$). The proportion of patients receiving adjuvant antiangiogenic therapy significantly differed between the low-, intermediate-, and high-risk subgroups (Supplementary Table 6).

4. Discussion

The main finding of our study is that GD (upgrading or downgrading) between the PT grade and the VTT grade is common (observed in approximately half of cases) and provides independent prognostic information after accounting for other clinicopathologic factors. Incorporating this unique attribute of ccRCC with VTT, we used data for patients who underwent complete surgical resection to develop GD-based nomograms for prediction of DFS, OS, and CSS. These nomograms could facilitate patient selection and improve counseling regarding adjuvant therapy.

Our study sheds some light on the prognostic impact of pathologic features. First, the risk of interaction, overfitting, and multicollinearity must be considered in predictive modeling of these variables, as they result in lower significance of a predictor when applied to a single data set [33]. The LASSO approach for optimal variable selection not only allows conversion of a panel of candidate features to a combined signature but also surpasses the method for selecting predictors according to the strength of their univariate asso-

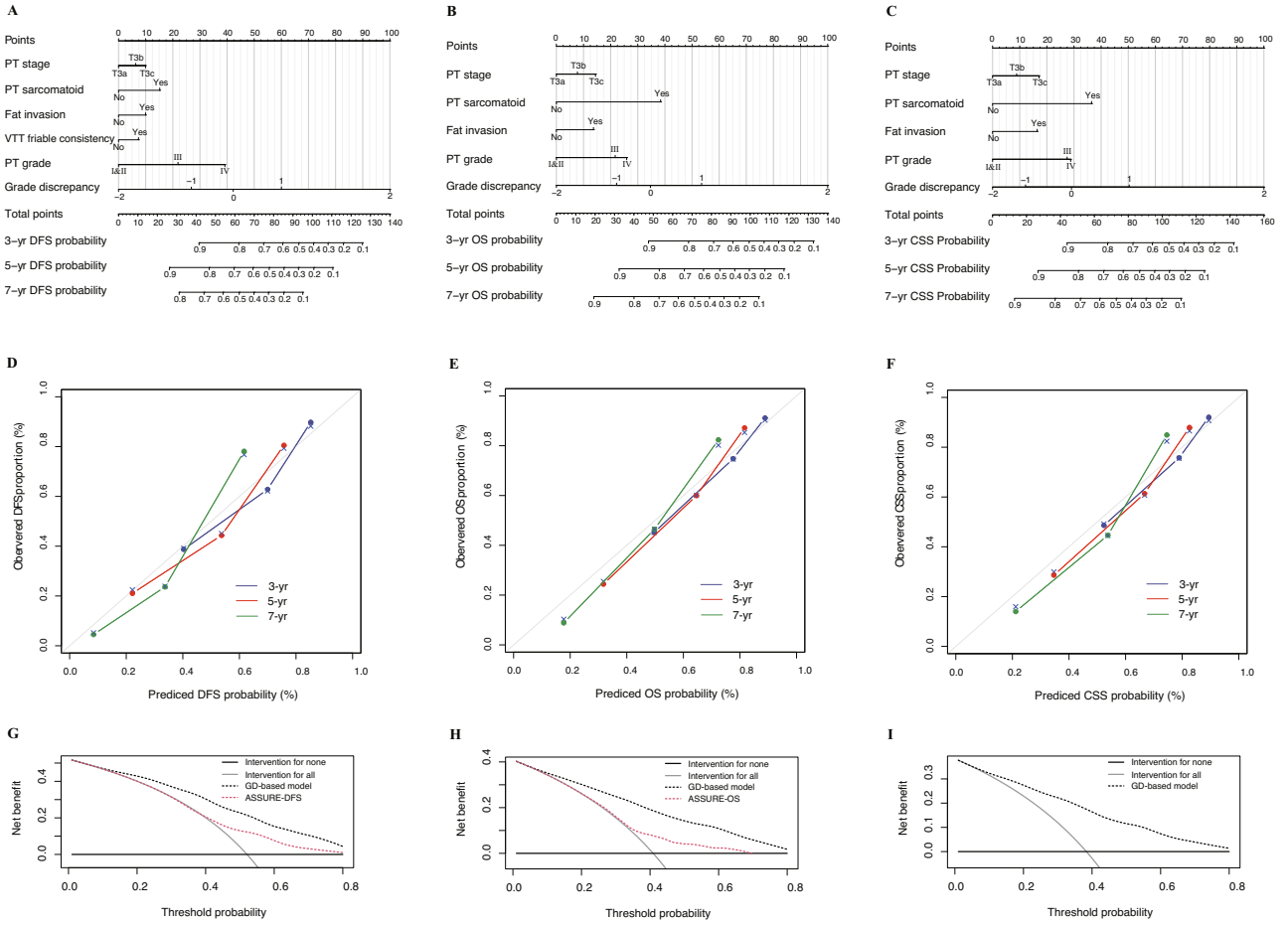

Fig. 3 – Nomograms and their calibration plots and decision curves for prediction of prognosis for (A,D,G) disease-free survival (DFS), (B,E,H) overall survival (OS), and (C,F,I) cancer-specific survival (CSS). Grade discrepancy (GD) was defined as the venous tumor thrombus grade minus the primary tumor grade.

Table 3 – GD-based model for the three survival endpoints (n = 604)

Risk factor	Disease-free survival		Overall survival		Cancer-specific survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Pathologic stage (vs pT3a)						
pT3b	1.26 (0.93–1.7)	0.14	1.32 (0.93–1.88)	0.12	1.32 (0.91–1.91)	0.14
pT3c	1.44 (1.06–1.95)	**0.020**	1.69 (1.19–2.38)	**0.003**	1.71 (1.19–2.45)	**0.004**
PT sarcomatoid (yes vs no)	1.72 (1–2.96)	**0.050**	3.97 (1.8–8.77)	**<0.001**	3.12 (1.46–6.63)	**0.003**
Fat invasion (yes vs no)	1.43 (1.11–1.85)	**0.009**	1.63 (1.22–2.17)	**<0.001**	1.67 (1.23–2.25)	**<0.001**
Thrombus consistency (friable vs solid)	1.31(1.03–1.66)	**0.03**	–	–	–	–
PT grade (vs I–II)						
III	2.21 (1.5–3.24)	**<0.001**	2.54 (1.61–3.99)	**<0.001**	2.35 (1.48–3.75)	**<0.001**
IV	4.12 (2.21–7.68)	**<0.001**	2.18 (0.91–5.22)	0.082	2.45 (1.05–5.7)	**0.038**
Grade discrepancy (vs 0)						
−2 (VTT downgrading by 2 classes)	0.22 (0.08–0.6)	**0.003**	0.29 (0.09–0.93)	**0.037**	0.41 (0.15–1.13)	0.085
−1 (VTT downgrading by 1 class)	0.57 (0.41–0.81)	**0.001**	0.64 (0.43–0.94)	**0.023**	0.59 (0.39–0.9)	**0.013**
1 (VTT upgrading by 1 class)	1.9 (1.37–2.63)	**<0.001**	1.97 (1.35–2.87)	**<0.001**	1.94 (1.3–2.88)	**0.001**
2 (VTT upgrading by 2 classes)	8.01 (3.86–16.6)	**<0.001**	10.4 (4.78–22.5)	**<0.001**	9.06 (4.05–20.2)	**<0.001**
Harrell's c index	0.72 (0.69–0.75)		0.74 (0.71–0.77)		0.74 (0.7–0.77)	

GD = grade discrepancy; PT = primary tumor; VTT = venous tumor thrombus; HR = hazard ratio; CI = confidence interval.

ciation with the outcome of interest [34,35]. In the present study, this method was successfully applied and identified six significant items: pT stage, PT sarcomatoid features, VTT consistency, PT grade, GD, and fat invasion. The coefficient was higher for the GD variable than for the other factors included in the nomogram, indicating a higher point increase for a 1-unit change.

Furthermore, the significant improvement in model performance (Supplementary Table 3) revealed that the best tumor grade to include is the combination of PT grade and

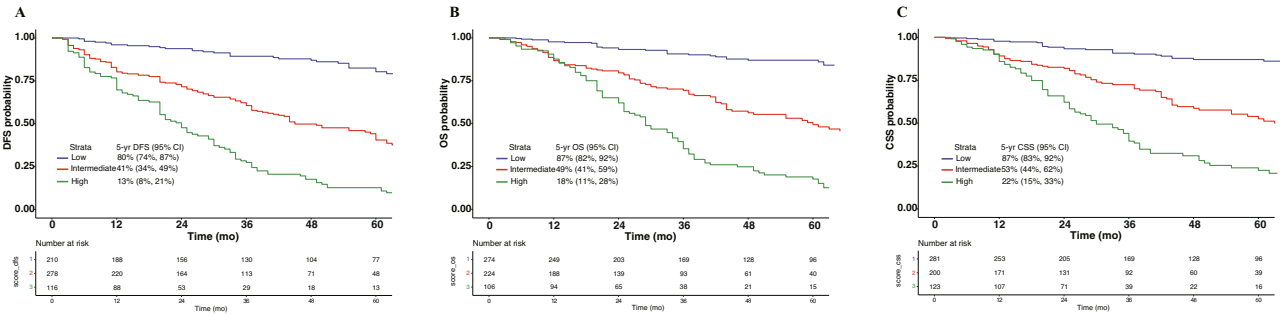

Fig. 4 – Kaplan-Meier estimates with Cox regression analysis for survival in low-risk, intermediate-risk, and high-risk subgroups: (A) disease-free survival (DFS), (B) overall survival (OS), and (C) cancer-specific survival (CSS). CI = confidence interval.

GD, rather than the highest PT-VTT grade as a single parameter. Because of the value of GD in risk stratification of patients and the ease of determining VTT grade, introduction of VTT grade assessment in routine histopathology reporting would be feasible and informative. Previous research demonstrated correlations and differences between PTs and VTTs at the molecular level and with respect to patterns of clonal evolution [22,23]. More specifically, evidence of phenotypic heterogeneity was found between PTs and tumor thrombi in terms of tumor cells, immune cells, and stromal cells. In addition, invasion may not necessarily be driven by the most aggressive subclones in the tumor, and rather than the most aggressive, the most invasive subclones appear to be the main determinants of metastatic competence. Recent analysis of the evolutionary routes from PT to VTT in ccRCC revealed that the mode of local progression (“front”-driven vs “rear”-driven) is associated with different metastatic events [36].

Finally, in concordance with others [17,18,37], we confirmed that perinephric or sinus fat invasion is an adverse prognostic factor independent of pathologic stage. In this regard, reclassification of the current pT3a stage to differentiate fat invasion from renal VTT should be considered.

The clinical usefulness of the nomograms was evaluated to facilitate patient selection and thereby improve the value proposition of adjuvant therapy for patients at high risk of recurrence. For instance, in our data set with a 5-year DFS rate of 48%, for a decision threshold of 50% for the probability of relapse 5 yr after surgery in comparison to a strategy of “intervention for none”, our nomogram would identify 23 additional true relapses (avoid undertreatment) within 5 yr per 100 subjects (net benefit 0.23) without increasing the number of false-positive (overtreatment) predictions, and would identify ten additional true relapses (avoid undertreatment) within 5 yr per 100 subjects in comparison to the ASSURE model (net benefit 0.1). In addition, in comparison to a strategy of “intervention for all”, our nomogram would avoid 20 false positives (avoid overtreatment) for unnecessary intervention within 5 yr per 100 subjects (net benefit = 0.23 − 0.03 = 0.2) at a threshold of 50% (harm-to-benefit ratio = 50% / (1 − 50%) = 1) without decreasing the number of true-positive predictions. Moreover, Cox regression analysis indicated that the risk cutoff based on our model was clinically significant. A recent study using a decision analytic Markov model found that adjuvant pembrolizumab would be cost effective at 5 yr only for patients with a 5-yr risk of progression of at least 59%. Our sensitivity analysis confirmed the association of GD with DFS probability in the subgroup of patients who did not receive adjuvant therapy and in whom the disease typically follows its natural course. GD as a potential prognostic factor can help in predicting the natural disease course for patients with ccRCC and VTT. Given the lack of predictive factors for adjuvant ICI therapy, reliance on prognostic factors is still the only practical strategy for selection of the patients most likely to benefit from an adjuvant treatment approach. Our prediction tool may be especially useful for treatment selection for candidates classified as having intermediate or high risk, for whom the 5-yr DFS probability was 0.41, and 0.13, respectively. Conversely, those who are at low risk of postoperative progression (5-yr DFS probability of 0.87) would probably benefit from active surveillance.

The main limitation of our study lies in its retrospective nature even though the data were collected in a structured form with centralized pathologic assessment and review of radiologic slides. First, the results are subject to inherent biases, particularly concerning the varied follow-up strategy among institutions (potential to affect survival outcomes, particularly DFS) and lack of information on the type of agents used for adjuvant therapy. Missing values for candidate predictive variables led to exclusion of cases, with a further decrease in study power. Nevertheless, only patients with a clear description of surgical assessment of venous thrombus height were included to ensure accurate evaluation of pathologic stage, since upstaging might occur because of the time lag between last imaging and surgery. Second, the generalizability of this multicenter study is limited because it only included patients with ccRCC, but the homogeneous inclusion criteria would improve the accuracy of individualized prediction and pinpoint the unmet need highlighted by the KEYNOTE-564 trial. Third, additional validation will be required to evaluate the utility of the nomograms for non-ccRCC and more advanced disease stages (pT4, N+, M+). Finally, the predictive value of grade discrepancy might be lower for tumor grade IV, since in this scenario only downgrading can occur, and even the presence of rhabdoid and or sarcomatoid features would be assessed as grade IV. Despite these limitations, this is the first study to assess the

impact of discrepancy between the PT grade and the VTT grade on prognosis, although external validation is required.

5. Conclusions

Grade discrepancy between the PT grade and the VTT grade is a common phenomenon in nonmetastatic ccRCC and is associated with prognosis. Routine reporting of VTT upgrading or downgrading and use of our GD-based nomograms can facilitate more informed treatment decisions about adjuvant therapy by tailoring it to the individual patient's risk of progression.

Author contributions: Zhenjie Wu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.06.006.

References

[1] Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med 2021;385:683–94.
[2] Powles T, Tomczak P, Park SH, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022;23:1133–44.
[3] Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. Lancet 2022;400:1103–16.
[4] Bedke J, Albiges L, Capitanio U, et al. The 2022 updated European Association of Urology guidelines on the use of adjuvant immune checkpoint inhibitor therapy for renal cell carcinoma. Eur Urol 2023;83:10–4.
[5] Sharma V, Wymer KM, Joyce DD, et al. Cost-effectiveness of adjuvant pembrolizumab after nephrectomy for high-risk renal cell carcinoma: insights for patient selection from a Markov model. J Urol 2023;209:89–98.
[6] Marchioni M, Amparore D, Marandino L, et al. Is adjuvant immunotherapy worth for all patients with clear-cell renal cell carcinoma at high risk of recurrence? Eur Urol Open Sci 2022;46:39–42.
[7] Correa AF, Jegede OA, Haas NB, et al. Predicting disease recurrence, early progression, and overall survival following surgical resection for high-risk localized and locally advanced renal cell carcinoma. Eur Urol 2021;80:20–31.
[8] Kattan MW, Reuter V, Motzer RJ, Katz J, Russo P. A postoperative prognostic nomogram for renal cell carcinoma. J Urol 2001;166:63–7.
[9] Yaycioglu O, Roberts WW, Chan T, Epstein JI, Marshall FF, Kavoussi LR. Prognostic assessment of nonmetastatic renal cell carcinoma: a clinically based model. Urology 2001;58:141–5.
[10] Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 2002;168:2395–400.
[11] Zisman A, Pantuck AJ, Wieder J, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 2002;20:4559–66.
[12] Cindolo L, de la Taille A, Messina G, et al. A preoperative clinical prognostic model for non-metastatic renal cell carcinoma. BJU Int 2003;92:901–5.
[13] Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 2003;97:1663–71.
[14] Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol 2005;173:48–51.
[15] Thompson RH, Leibovich BC, Lohse CM, et al. Dynamic outcome prediction in patients with clear cell renal cell carcinoma treated with radical nephrectomy: the D-SSIGN score. J Urol 2007;177:477–80.
[16] Karakiewicz PI, Suardi N, Capitanio U, et al. A preoperative prognostic model for patients treated with nephrectomy for renal cell carcinoma. Eur Urol 2009;55:287–95.
[17] Abel EJ, Masterson TA, Karam JA, et al. Predictive nomogram for recurrence following surgery for nonmetastatic renal cell cancer with tumor thrombus. J Urol 2017;198:810–6.
[18] Tilki D, Nguyen HG, Dall'Era MA, et al. Impact of histologic subtype on cancer-specific survival in patients with renal cell carcinoma and tumor thrombus. Eur Urol 2014;66:577–83.
[19] Whitson JM, Reese AC, Meng MV. Population based analysis of survival in patients with renal cell carcinoma and venous tumor thrombus. Urol Oncol 2013;31:259–63.

[20] Abel EJ, Wood CG, Eickstaedt N, et al. Preoperative pulmonary embolism does not predict poor postoperative outcomes in patients with renal cell carcinoma and venous thrombus. J Urol 2013;190:452–7.
[21] Bertini R, Roscigno M, Freschi M, et al. Impact of venous tumour thrombus consistency (solid vs friable) on cancer-specific survival in patients with renal cell carcinoma. Eur Urol 2011;60:358–65.
[22] Shi Y, Zhang Q, Bi H, et al. Decoding the multicellular ecosystem of vena caval tumor thrombus in clear cell renal cell carcinoma by single-cell RNA sequencing. Genome Biol 2022;23:87.
[23] Kim K, Zhou Q, Christie A, et al. Determinants of renal cell carcinoma invasion and metastatic competence. Nat Commun 2021;12:5760.
[24] Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab for postnephrectomy renal cell carcinoma (RCC): expanded efficacy analyses from KEYNOTE-564. J Clin Oncol 2022;40(16 Suppl):4512.
[25] Moch H, Amin MB, Berney DM, et al. The 2022 World Health Organization classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. Eur Urol 2022;82:458–68.
[26] Delahunt B, Cheville JC, Martignoni G, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol 2013;37:1490–504.
[27] Rodriguez Faba O, Linares E, Tilki D, et al. Impact of microscopic wall invasion of the renal vein or inferior vena cava on cancer-specific survival in patients with renal cell carcinoma and tumor thrombus: a multi-institutional analysis from the International Renal Cell Carcinoma-Venous Thrombus Consortium. Eur Urol Focus 2018;4:435–41.
[28] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[29] Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the eighth edition of the tumor-node-metastasis staging classification for urologic cancers. Eur Urol 2018;73:560–9.
[30] Moons KG, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1–W.
[31] Kattan MW, Hess KR, Amin MB, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. CA Cancer J Clin 2016;66:370–4.
[32] Kang L, Chen W, Petrick NA, Gallas BD. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. Stat Med 2015;34:685–703.
[33] Cook JA, Ranstam J. Overfitting. Br J Surg 2016;103:1814.
[34] Steyerberg EW, Eijkemans MJ, Harrell Jr FE, Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19:1059–79.
[35] Tibshirani R. Regression shrinkage and selection via the Lasso. J R Stat Soc Ser B 1996;58:267–88.
[36] Xie R, Sun H, Zhao S, et al. Front- and rear-driving patterns of tumor thrombus progression in clear cell renal cell carcinoma. Eur Urol 2022;82:446–8.
[37] Shah PH, Lyon TD, Lohse CM, et al. Prognostic evaluation of perinephric fat, renal sinus fat, and renal vein invasion for patients with pathological stage T3a clear-cell renal cell carcinoma. BJU Int 2019;123:270–6.