

# Podoplanin associates with adverse postoperative prognosis of patients with clear cell renal cell carcinoma

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## Key words

Clear cell renal cell carcinoma, overall survival, podoplanin, prognostic biomarker, recurrence free survival

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Renal cell carcinoma (RCC) is the most common type of malignant tumor in the adult kidney and represents 2–3% of all adult cancers. Annually, it causes approximately 102 000 deaths around the world. Clear cell renal cell carcinoma (ccRCC) is the major histologic subtype of RCC (75–85%), and more than one-tenth of patients with this disease experience fatal recurrence within 5 years after traditional partial or radical nephrectomy.<sup>(1)</sup> Owing to the complicated molecular heterogeneity in tumors, current TNM stage and several clinical integrated prognostic models are not enough for ccRCC outcome prediction.<sup>(2)</sup> Adding specific molecular information to these models might help with ccRCC patients' risk stratification and survival prediction.<sup>(3)</sup>

Podoplanin, a transmembrane sialomucin-like glycoprotein, was initially identified as a specific marker for lymphatic

endothelial cells and as being important for embryonic development. Apart from its usage in tumor lymphatic invasion assessment, in recent years, the expression of podoplanin in cancer cells has also gained considerable attention for its potential role in tumor progression and metastasis.<sup>(4)</sup> Several studies have identified that this molecule could work as a powerful platelet aggregator by binding to the platelet C-type lectin receptor, CLEC-2, through its sialylated platelet aggregation stimulating (PLAG) domain and subsequent mediating tumor embolization formation, immunosurveillance evasion and distant metastasis.<sup>(5,6)</sup> Podoplanin is also involved in the epithelial-to-mesenchymal transition (EMT) and collective-cell migration functions of various cell lines.<sup>(7,8)</sup> Upregulation of podoplanin has been found in many malignancies, including several squamous cell carcinomas, mesothelioma, vascular

tumors, germ cell tumors, bone tumors and brain tumors, and in most cases predicts an adverse outcome.<sup>(9)</sup>

Because podoplanin can facilitate tumor invasion and metastasis through diverse molecular patterns as mentioned above, in the present study we investigated whether this molecule could become a potential prognostic marker for ccRCC patients. Here, through immunohistochemistry (IHC), we investigated the expression of intratumoral podoplanin in a large cohort of ccRCC patients ( $n = 295$ ) and analyzed the impact of podoplanin expression on their survival. Two nomograms were formed to predict patients' overall survival (OS) and recurrence-free survival (RFS) based on tumoral podoplanin expression and other clinical parameters.

## Materials and Methods

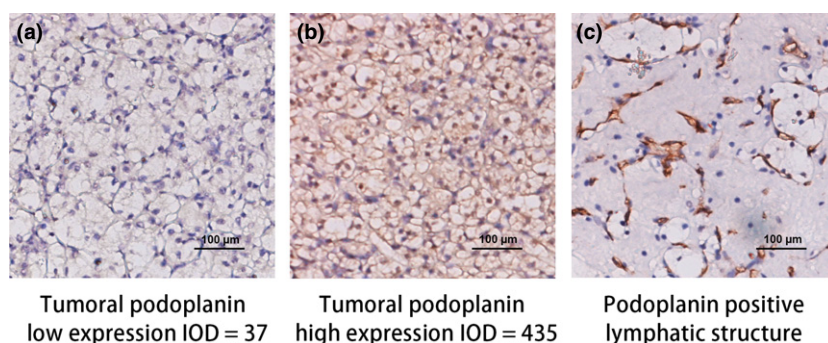
**Patient selection.** We retrospectively recruited 295 ccRCC patients who underwent nephrectomy between January 2005 and June 2007 from the Department of Urology, Zhongshan Hospital, Fudan University. Approval for the study was granted by the hospital's ethics committee (approval number B2015-030) and informed consent was obtained from all individuals. All procedures conformed to the provisions of the Declaration of Helsinki. The inclusion criteria were as follows: (i) patients with ccRCC diagnosed pathologically; (ii) patients who have received partial, radical or cytoreductive nephrectomy; and (iii) patients who had enough formalin fixed paraffin embedded tumor specimens for analysis. We excluded patients who had a history of malignancy, perioperative mortalities or those who had received targeted therapies before or after the surgery. Patients with mixed type renal cancer, bilateral renal cancer and tumor necrosis area in the formalin-fixed, paraffin-embedded samples >80% were also excluded.

**Data collection.** Patients' OS and RFS were selected as the study outcomes. OS was defined as the time from nephrectomy to the time of death. RFS was calculated from the time of nephrectomy to the time of recurrence (local or distant lesions confirmed by imaging or biopsy after the surgery). Patients were followed up every 3 months during the first 5 years and annually thereafter. A total of 15 patients were excluded in the RFS analysis for preoperational metastases. RFS data were censored if recurrence did not occur during the follow-up period and OS data were censored if patients lived till the last follow-up (30 January 2015). We have verified all the baseline clinical and laboratory data of the patients. According to the 2014 EAU guidelines<sup>(10)</sup> and the 2012 ISUP consensus,<sup>(3)</sup> two urologic pathologists (Yuan J. and Jun H.) independently reviewed all the HE slides of patient samples and confirmed the ccRCC diagnosis, Fuhrman grade classification and coagulative necrosis status. Based on the 2010 AJCC TNM classification,<sup>(11)</sup> patients'

computed tomography, magnetic resonance imaging scans and pathological information were used to define the TNM stage or recurrence. The Mayo Clinic stage, size, grade and necrosis score (SSIGN),<sup>(12)</sup> the University of California Integrated Staging System (UISS)<sup>(13)</sup> and the SSIGN localized (Leibovich)<sup>(14)</sup> score were applied to stratify patient risks, as previously reported.

**Immunohistochemistry and evaluation.** Tissue microarray (TMA) was constructed based on patients' tumor samples. Anti-podoplanin antibody (ab10288; Abcam, 330 Science Park, Cambridge CB4 0FL, England, United Kingdom, diluted 1/1000) and Dako EnVision Detection System were applied in the immunohistochemistry procedure as previously described.<sup>(15)</sup> Through western blot analysis of RCC cell lines, the specificity of the antibody was confirmed. The negative control was performed using the same IHC procedure without applying a primary antibody. An Olympus CDD (Shinjuku Monolith, 3-1 Nishi-Shinjuku 2-chome, Shinjuku-ku, Tokyo 163-0914, Japan) camera, a Nikon (Shinagawa Intercity Tower C, 2-15-3, Konan, Minato-ku, Tokyo 108-6290, Japan) eclipse Ti-s microscope ( $\times 200$  magnification) and the NIS-Elements F3.2 software package were used to record the staining results. Two cores for each tumor sample were selected for TMA construction, and three independent shots with the strongest staining of each core were recorded for the final analysis. Using Image-Pro Plus version 6.0 (Media Cybernetics, Bethesda, MD, USA), an integrated optical density (IOD) score was calculated for each scan, and the pooled IOD mean of each sample's six scans was regarded as the final staining intensity. One urologic pathologist unaware of the patients' clinical features and outcomes evaluated these slides.

**Statistical analysis.** To determine the prognostic significance of tumoral podoplanin expression and several other clinical characteristics, univariate analysis was carried out, using the podoplanin IOD score as a continuous variable. The smooth estimates of the hazard ratio and 95% confidential intervals of the podoplanin IOD score on patient survival were displayed using R software ("phenoTest" package). Those parameters with statistical significance were entered into a multivariate Cox proportional hazards model and 1000 bootstrap resamples were performed to reduce overfitting bias. The IOD cut-off point of high/low podoplanin expression was chosen using the minimum *P*-value method and x-tile software, and illustrated using R software ("smoothHR" package). After this, Kaplan-Meier analysis and a log-rank test were performed to detect the survival differences between patient groups and the UISS system was used for stratified analysis. Cox multivariate analysis using podoplanin expression as a dichotomous variable was also carried out and two nomograms were formed for predicting ccRCC patients' 5- or 8-year OS and RFS after surgery. The concordance index (c-index) was generated to assess the predictive accuracy and sufficiency of different models, while Hanley-McNeil test was



**Fig. 1.** Representative photographs of podoplanin immunostaining in clear cell renal cell carcinoma (ccRCC). (a) Tumoral podoplanin low expression; (b) tumoral podoplanin high expression; and (c) podoplanin-positive lymphatic structures with tumor invasion. Original magnification  $\times 200$ .

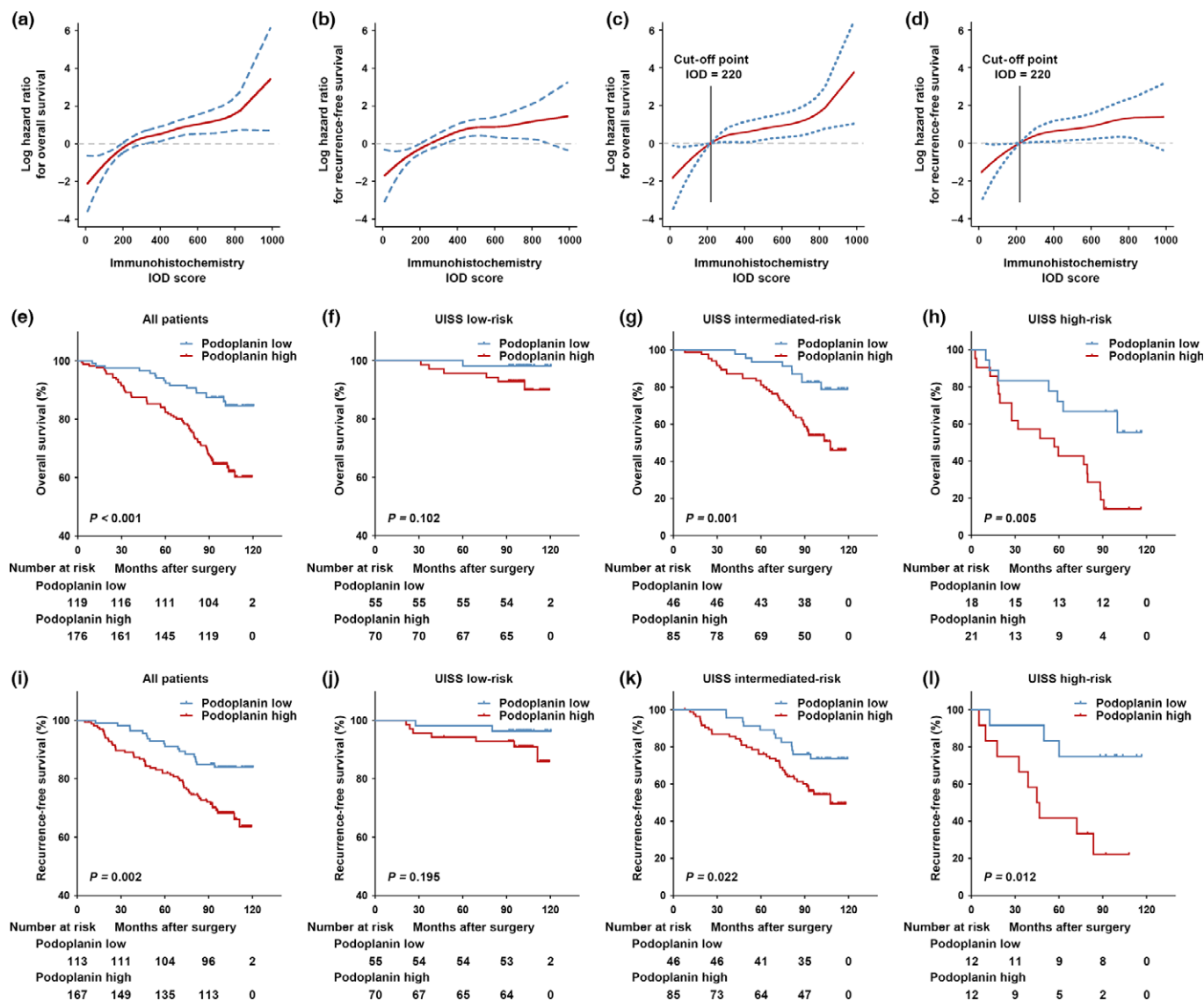
applied to compare the difference between c-indexes. GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA), SPSS 21.0 (SPSS, IL, Chicago, USA), Stata (version 12.1; StataCorp College Station, LP, TX, USA), X-tile<sup>(16)</sup> (version 3.6.1; Robert L Camp, Yale University, CT, USA) and R software version 3.1.2 with the “smoothHR,”<sup>(17)</sup> “phenoTest”<sup>(18)</sup> and “rms” package (R Foundation for Statistical Computing, Vienna, Austria) were used for these procedures. A two-sided *P*-value <0.05 was regarded as statistically significant.

## Results

**Podoplanin staining in clear cell renal cell carcinoma and peritumoral tissue.** The intensity of podoplanin expression in

ccRCC tissue was variable, and this molecule was mostly expressed on the membrane and cytoplasm of tumor cells (Fig. 1b). We also found some podoplanin-positive lymphatic like structures at the invasive front of tumor tissue, which was in accord with several other reports (Fig. 1c)<sup>(19,20)</sup> The IOD distributions of podoplanin expression in 295 ccRCC samples were 10–990 for range;  $291 \pm 170$  for mean and SD; and 252 (178–387) for median and IQR.

**Clinical characteristics and patient outcomes.** Patients’ basic clinical characteristics are shown in Table S1. The median follow up for all 295 patients was 98.97 months (range 2.63–120.47). Of the 295 patients, 82 (27.8%) died during the follow up period and 71 of 280 patients (25.4%) experienced disease relapse. A total of 15 patients were diagnosed with



**Fig. 2.** The impact of tumoral podoplanin expression on patients’ overall survival (OS) and recurrence-free survival (RFS) and University of California Integrated Staging System (UISS) score based stratified analysis. (a, b) Smooth estimates of HR (+1 IOD) showed a higher risk of death and recurrence for patients with stronger tumoral podoplanin staining. (c, d) Smooth estimates of HR (using IOD = 220 as a reference) showed a significant and stable prognostic difference between patients with high/low tumoral podoplanin staining. Dashed lines: 95% confidence bands. (e) Overall survival (OS) of all clear cell renal cell carcinoma (ccRCC) patients according to tumoral podoplanin high/low expression. (f–h) OS of patients in different UISS risk groups according to tumoral podoplanin high/low expression. (i) RFS of all available ccRCC patients according to tumoral podoplanin high/low expression. (j–l) RFS of patients in different UISS risk groups according to tumoral podoplanin high/low expression. *P*-value, calculated by log rank test, <0.05 was regarded as statistically significant.

metastatic RCC before the surgery and received cytoreductive nephrectomy.

**Survival analyses using tumoral podoplanin expression as a continuous variable.** To explore the potential prognostic significance of tumoral podoplanin expression on patient survival, univariate analysis was conducted using the podoplanin IOD score as a continuous variable (Table S2). The smooth estimated HR of tumoral podoplanin expression (+1 IOD score) on patient OS and RFS is illustrated in Figure 2(a,b). The results suggest tumoral podoplanin expression as a significant adverse prognostic marker for ccRCC patients' OS and RFS prediction ( $P < 0.001$  for both). A multivariate Cox proportional hazards model was further carried out (Table S3). Patient age and tumor size were excluded for not meeting statistical significance in the new model, and TNM stage was excluded for being a potential confounder for pT and pM stage. The result still demonstrated an independent adverse prognostic role of tumoral podoplanin expression on patient OS and RFS (OS, HR, 1.003, 95% CI, 1.002–1.004,  $P < 0.001$ ; RFS, HR, 1.003, 95% CI, 1.002–1.005,  $P < 0.001$ ), even after a 1000-resampled bootstrap for reducing overfitting bias (OS, HR, 1.003, 95% CI, 1.001–1.004,  $P < 0.001$ ; RFS, HR, 1.003, 95% CI, 1.000–1.004,  $P < 0.001$ ), together with pTstage, distant metastasis, Fuhrman grade, necrosis and Eastern Cooperative Oncology Group Performance Status (ECOG PS).

**Survival analyses using tumoral podoplanin expression as a dichotomous variable.** For convenience in clinical usage, we simplified the podoplanin IOD score, which was originally a continuous variable, into a dichotomous variable (high/low

expression). Through minimum  $P$ -value method, IOD = 220 was chosen as the cut-off point. The smooth HR curve displayed a significant and stable prognostic difference between the high and low podoplanin expression patient groups (Fig. 2c,d). Survival analysis using the Kaplan–Meier method suggested that ccRCC patients with high tumoral podoplanin expression had significantly poorer OS ( $P < 0.001$ ) and RFS ( $P = 0.002$ ) (Fig. 2e,i). Multivariate analysis incorporating tumoral podoplanin as high/low expression also confirmed its independent prognostic role (OS, HR, 2.743, 95% CI, 1.603–4.694,  $P < 0.001$ ; RFS, HR, 2.355, 95% CI, 1.362–4.071,  $P = 0.002$ ; OS after 1000 bootstrap, HR, 2.989, 95% CI, 1.568–6.366,  $P = 0.004$ ; RFS after 1000 bootstrap, HR, 2.570, 95% CI, 1.103–5.222,  $P = 0.036$ ) (Table 1). For stratified analysis, the UISS score was applied to classify patients into three risk levels: low (UISS I), intermediate (UISS II) and high (UISS  $\geq$  III, combining the original high risk group of localized disease patients [UISS = III] with the metastatic patient group [UISS  $>$  III]). As is evident from Figure 2f–h,j,l, high tumoral podoplanin expression was an adverse prognostic factor in the intermediate-risk and high-risk groups in both OS and RFS analyses (OS,  $P = 0.001$ , RFS,  $P = 0.005$  in intermediate -risk groups; OS,  $P < 0.022$ , RFS,  $P < 0.012$  in high-risk groups), while in the low-risk groups it did not meet statistical significance.

**Predictive impact of tumoral podoplanin upon different prognostic models and nomograms formation.** As shown in Table 2, tumoral podoplanin expression information could add additional power to several existing RCC prognostic models (OS,  $P = 0.004$ , RFS,  $P = 0.014$  for TNM; OS,  $P = 0.044$ , RFS,  $P = 0.033$  for SSIGN). In UISS risk stratification, this

**Table 1.** Proportional hazard model for overall survival and recurrence-free survival prediction using tumoral podoplanin expression as a dichotomous variable

Variables	OS ( $n = 295$ )				RFS ( $n = 280$ )			
	Base model		Bootstrap validate model†		Base model		Bootstrap validate model†	
	HR (95% CI)	$P$ -value‡	HR (95% CI)	$P$ -value‡	HR (95% CI)	$P$ -value‡	HR (95% CI)	$P$ -value‡
Pathological T stage		<0.001		0.005		<0.001		0.002
pT2 versus pT1	2.984 (1.498–5.941)	0.002	2.898 (1.221–6.372)	0.007	2.196 (0.994–4.851)	0.052	2.373 (0.945–6.032)	0.098
pT3 versus pT1	3.133 (1.872–5.243)	<0.001	3.146 (1.551–6.007)	0.002	2.587 (1.489–4.496)	0.001	2.578 (1.203–5.033)	0.009
pT4 versus pT1	7.211 (1.986–26.249)	0.003	7.142 (0.000–78.295)	0.107	14.621 (4.535–47.139)	<0.001	16.643 (1.000–93.253)	0.002
Distant metastasis								
Yes versus no	3.460 (1.751–6.838)	<0.001	4.609 (1.511–22.220)	0.047	—	—	—	—
Fuhrman grade		0.002		0.003		<0.001		0.001
3 vs 1–2	1.974 (1.089–3.582)	0.025	2.166 (1.001–4.721)	0.072	2.775 (1.492–5.160)	0.001	2.838 (1.032–5.918)	0.005
4 vs 1–2	5.879 (1.730–19.983)	0.005	6.713 (2.656–21.999)	0.001	6.434 (1.866–22.179)	0.003	6.706 (1.000–21.802)	0.001
Necrosis								
Present versus absent	1.945 (1.070–3.536)	0.029	2.030 (0.985–4.080)	0.057	1.834 (0.986–3.411)	0.055	1.893 (0.915–4.059)	0.089
ECOG PS		<0.001		0.007		<0.001		0.008
1 vs 0	2.542 (1.543–4.186)	<0.001	2.529 (1.247–4.754)	0.003	2.109 (1.198–3.712)	0.010	2.175 (1.052–4.446)	0.032
2 vs 0	2.781 (1.093–7.075)	0.032	3.001 (0.541–10.740)	0.125	3.725 (1.303–10.650)	0.014	3.007 (1.004–12.085)	0.014
3 vs 0	4.556 (1.294–16.035)	0.018	4.129 (0.000–19.453)	0.012	6.088 (1.945–19.059)	0.002	7.854 (1.000–48.717)	0.021
Tumoral podoplanin								
Low versus high	2.743 (1.603–4.694)	<0.001	2.989 (1.568–6.366)	0.004	2.355 (1.362–4.071)	0.002	2.570 (1.103–5.222)	0.036

†Bootstrapping with 1000 resamples were used; ‡Data obtained from the Cox proportional hazards model;  $P$ -value  $< 0.05$  was regarded as statistically significant. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival.

dichotomous variable could also display a marginal additional prognostic effect (OS,  $P = 0.085$ , RFS,  $P = 0.096$ ).

After utilizing those parameters in the validated multivariate analysis, two nomograms for predicting 5-year and 8-year ccRCC patients' OS and RFS were established, involving pT stage, distant metastasis, Fuhrman grade, necrosis status, ECOG PS and tumoral podoplanin as high/low expression (Fig. 3a,b). Bootstrap validations were performed to examine the robustness of these models and the calibration plots displayed good consistency between the predicted and actual observation of patient survival (Fig. 3c–f). The Harrell's c-index was 0.815 (95% CI, 0.774–0.856) and 0.805 (95% CI, 0.755–0.855) for OS and RFS prediction, respectively. Comparison of the established nomograms with SSIGN or UISS also indicated nomograms as a better prognostic model for ccRCC patient survival prediction in both the all patient groups and intermediate/high risk patient groups ( $P < 0.001$  for all) (Table 2). All the SSIGN, SSIGN localized (Leibovich) and UISS stratifications were used in the original 0–15, 0–11 and I–VI score forms for podoplanin expression integration and model comparisons.

## Discussion

In this study, high tumoral podoplanin expression has been identified as an independent adverse prognostic factor for ccRCC patients. This finding is in accord with most other published studies, although several reports consider it to be a favorable prognosticator.<sup>(9)</sup> After using UISS score for stratification, podoplanin's survival prediction value was more significant in the intermediate/high risk patient groups, suggesting its potential role in the later stages of ccRCC development, such as invasion and metastasis. Two nomograms were formed and performed better than existing clinical prognostic models for patients' OS and RFS prediction. Considering the heterogeneity of ccRCC and its unpredictable natural history, these two biomarker-based nomograms might be useful in patients'

risk stratification for potential recurrence, metastasis and overall survival.

Hematogenous metastasis is the commonest metastatic approach for renal cell carcinoma, which would lead to a dramatic decrease of patients' overall survival (5-year survival rate 91.8% for localized disease and 12.3% for advanced or metastatic disease according to SEER Cancer Statistics Factsheets).<sup>(21)</sup> During this procedure, platelet aggregation is proposed to be one of the important mechanisms facilitating initial tumor embolization and protecting tumor cells from shear stress and immunosurveillance.<sup>(22)</sup> The podoplanin aberrant upregulation has been reported in various cancer types,<sup>(9)</sup> and it has recently been identified as an important stimulator of platelet aggregation which leads to tumor pulmonary metastasis. This process is mediated by the sialylated O-glycans on the PLAG domain of this protein and its specific binding to the platelet expressed CLEC-2.<sup>(6)</sup> Thus, the adverse prognostic effect of tumoral podoplanin on ccRCC patients' OS and RFS in the present study might be partially due to the platelet-related pro-metastatic potency of this molecule.

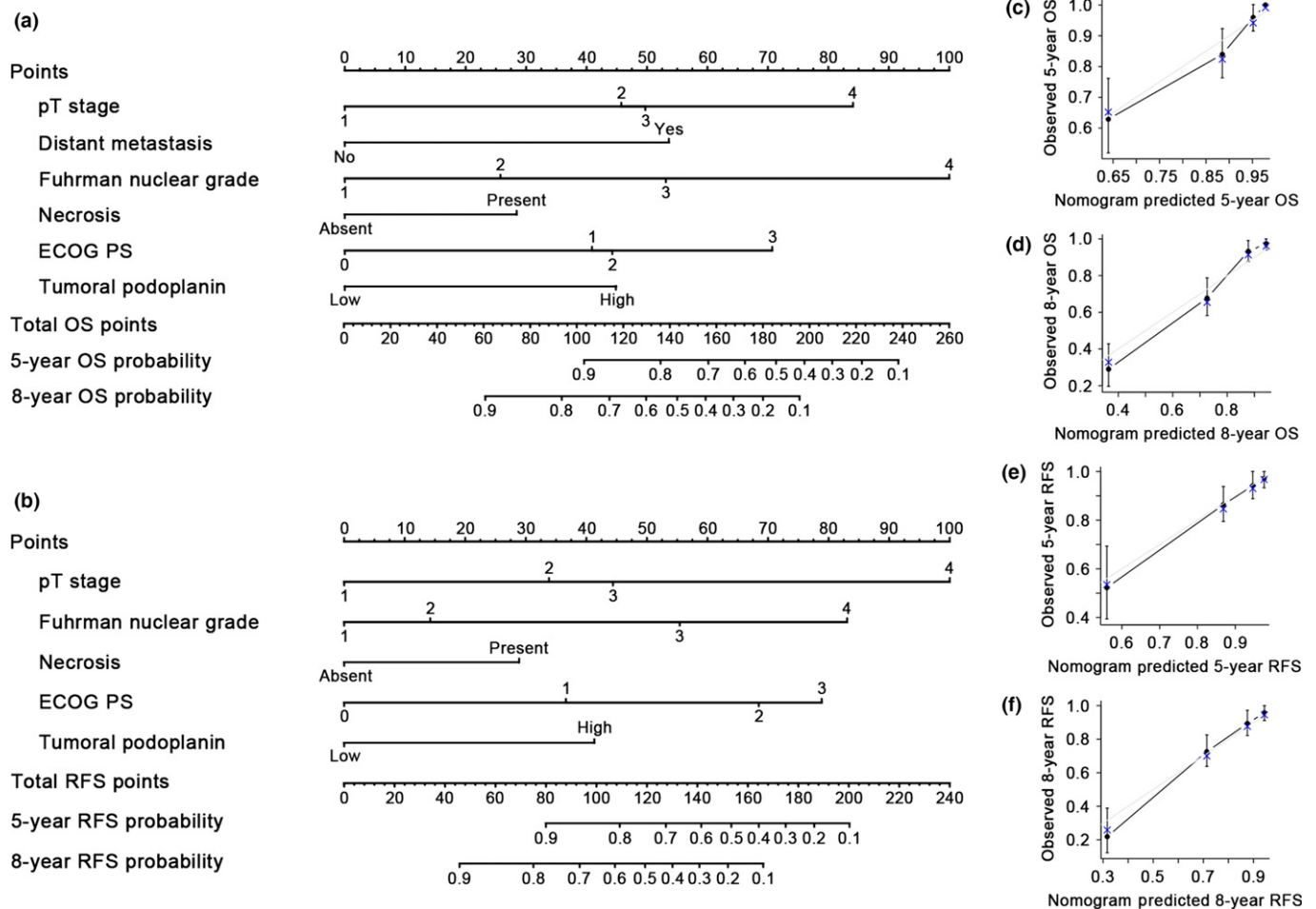
Several other pro-invasion mechanisms have been found to be related to podoplanin, one of which is EMT. It was identified that podoplanin could regulate the ezrin, radixin and moesin (ERM) proteins, RhoA and E-cadherin expression and subsequently mediate the promigratory phenotype of cancer cells.<sup>(7)</sup> Moreover, Wicki *et al.*<sup>(8)</sup> found that podoplanin could induce cancer cells into a collective-cell migration like phenotype, through the formation of filopodia and cell polarization, b1-integrin-mediated cell spreading and MMP-dependent cell invasion.

Besides its significance in regards to prognosis and cancer progression, the value of podoplanin in cancer treatment has also drawn increasing attention in recent years, as the inhibition of podoplanin-CLEC-2 interaction may not affect physiological homeostasis.<sup>(23)</sup> The blockage of podoplanin glycosylation by dietary lectins could inhibit tumor cell growth and motility.<sup>(24)</sup> Immunotoxin agents such as NZ-1 and human

**Table 2.** Comparison of the predictive accuracy of the prognostic models

Models	Overall survival			Recurrence-free survival		
	C-index (95% CI)	Coefficient (95% CI)	P-value	C-index (95% CI)	Coefficient (95% CI)	P-value
Tumoral Dectin-1	0.649 (0.606–0.692)	—	—	0.639 (0.590–0.687)	—	—
TNM	0.665 (0.611–0.718)	—	—	0.661 (0.602–0.720)	—	—
TNM + tumoralpodoplanin	0.734 (0.686–0.782)	0.069 (0.045–0.093)	0.004†	0.724 (0.668–0.779)	0.063 (0.038–0.088)	0.014†
SSIGN	0.724 (0.671–0.778)	—	—	0.716 (0.663–0.770)	—	—
SSIGN + tumoralpodoplanin	0.770 (0.721–0.819)	0.045 (0.023–0.067)	0.044†	0.758 (0.707–0.809)	0.042 (0.022–0.062)	0.033†
UISS	0.746 (0.699–0.792)	—	—	0.717 (0.666–0.768)	—	—
UISS + tumoralpodoplanin	0.785 (0.739–0.830)	0.039 (0.016–0.062)	0.085†	0.759 (0.709–0.810)	0.042 (0.017–0.067)	0.096†
Nomogram	0.815 (0.774–0.856)	—	—	0.805 (0.755–0.855)	—	—
Nomogram versus SSIGN						
In all patients	—	0.091 (0.069–0.113)	<0.001‡	—	0.089 (0.063–0.115)	<0.001‡
In SSIGN intermediate/high groups	—	0.099 (0.063–0.135)	<0.001‡	—	0.199 (0.159–0.239)	<0.001‡
Nomogram versus UISS						
In all patients	—	0.069 (0.053–0.085)	<0.001‡	—	0.089 (0.071–0.107)	<0.001‡
In UISS intermediate/high groups	—	0.130 (0.016–0.100)	<0.001‡	—	0.192 (0.161–0.223)	<0.001‡

†Compared the C-index with the original model without tumoral podoplanin expression data; ‡Compared the C-index of nomogram with SSIGN/UISS stratification in different patient groups. C-index, concordance index; CI, confidence interval; SSIGN, Mayo clinic stage, size, grade and necrosis score; UISS, UCLA Integrated Staging System. C-index and 95% CI were calculated from 1000 bootstrap samples to protect from overfitting.



**Fig. 3.** Nomogram for predicting 8-year and 5-year overall survival (OS) and recurrence free survival (RFS) in patients with clear cell renal cell carcinoma (ccRCC). (a) Nomogram for predicting ccRCC patient overall survival (OS) integrating pT stage, distant metastasis, Fuhrman nuclear grade, necrosis, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and tumoral podoplanin expression. (b) Nomogram for predicting ccRCC patient RFS integrating pT stage, Fuhrman nuclear grade, necrosis, ECOG PS and tumoral podoplanin expression. (c–f) Calibration plot for predicted and observed OS and RFS rate. Grey line: ideal model. Vertical bars: 95% confident interval.

chimeric antibodies ChMS-1 or ChP2-0 could suppress tumor progression and metastasis through the blockage of podoplanin-induced platelet aggregation.<sup>(25–27)</sup> All these agents are promising for future clinical examinations of podoplanin-based targeted therapy for ccRCC treatment.

In this study, we focused on analyzing the tumoral expression of podoplanin and did not pay attention to the stromal area, although several reports suggest that podoplanin-positive cancer-associated fibroblast infiltration could also have prognostic significance in cancer patient survival.<sup>(28)</sup> Moreover, a prior study identified the adverse prognostic significance of podoplanin-positive lymphatic invasion in RCC patients.<sup>(19)</sup> Several other limitations of the present study warrant further discussion. This is a retrospective study in nature with a small, single-center patient group. A prospective, multicenter study with a larger sample size is necessary for further external validation. Basic laboratory studies are also required to investigate the detailed roles of podoplanin in ccRCC cells and its interaction with the tumor microenvironment.

In conclusion, our findings demonstrated that high tumoral podoplanin expression was an independent adverse prognostic factor for the RFS and OS of ccRCC patients. Nomograms

integrating tumoral podoplanin expression and other pathologic factors might improve the post-operative management of ccRCC patients. Further functional studies are required to identify the detailed role of podoplanin in ccRCC and its therapeutic potential.

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### Disclosure Statement

The authors have no conflict of interest to declare.

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Table S1.** Patient clinical characteristics.

**Table S2.** Univariate analyses of characteristics associated with overall survival and recurrence-free survival.

**Table S3.** Proportional hazard model for overall survival and recurrence-free survival prediction using tumoral podoplanin expression as a continuous variable.