External Validation of TNM-C Score in Three Community Hospital Cohorts for Clear Cell Renal Cell Carcinoma

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Abstract. *Aim: To assess the general applicability of TNM-C scoring, which consists of TNM classification and preoperative C-reactive protein concentration, the predictive ability of the TNM-C score was externally validated for patients with clear cell renal cell carcinoma (ccRCC) at three community hospitals. Patients and Methods: Seven hundred patients underwent radical or partial nephrectomy after being diagnosed with RCC. Out of the 700 patients, 518 with clear cell carcinoma served as the current study cohort. The predictive ability of the TMN-C score for cancer-specific survival (CSS) was estimated using Harrell's concordance index (c-index). Results: The c-index of the TNM-C score was 0.85 in the entire data set. CSS rates were clearly stratified according to the scoring model (p<0.001). Conclusion: Since TNM-C score alone (without pathological details) has a high predictive ability for the prognosis of ccRCC patients, it is generally applicable for use in community hospitals.*

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies (1). The incidence of RCC has increased over the last two decades among men and women in all regions and ethnic groups (2). The survival rate of patients with RCC is closely-related to their initial stage at-diagnosis. The five-year survival rate is 50% to 90% for localized disease, decreasing to 0% to 13% for metastatic disease (3). Although the prognosis of localized RCC after curative surgery is better, 30% of patients with curative surgery will eventually experience metastasis during the course of the disease (4). Patients with metastatic RCC have the worst prognosis, with a median survival length of only 12 months. An accurate prediction of outcome for patients with RCC treated with nephrectomy is critically important in patient counseling, in the stratification of patients for clinical trials of novel therapeutic approaches, and in the development of an appropriate postoperative surveillance program.

Several prognostic models have recently been proposed for predicting outcome following nephrectomy for patients suffering from RCC (5-7). However, many of the models require detailed pathological information, like a Fuhrman nuclear grade and tumor necrosis, which are not routinely reported in some hospitals, and features with less objectivity, such as performance status and clinical presentation. We, therefore, developed a simple model to predict for prognosis of clear cell RCC (ccRCC) using the TNM-C score, which requires only the TNM classification and preoperative C-reactive protein (CRP) concentration (8). The TNM-C score has already been validated by a referred center cohort with a high concordance index (c-index) of 0.865. Although the model is simple and easily available, its usefulness remains unclear, even in community hospitals. Thus, we investigated the applicability and predictive accuracy of the TNM-C score by validating it externally through the use of cohorts from three community hospitals in this retrospective study.

Patients and Methods

Patient selection. The patient population consisted of 700 patients with RCC who underwent radical or partial nephrectomy at the Tsuchiura Kyodo General Hospital (n=224), the Toride Kyodo General Hospital (n=161), and the Saitama Red Cross Hospital (n=315) between 1986 and 2009. Out of the 700 patients, 182 were excluded from the study due to lack of a preoperative CRP measurement (n=116), a pathological condition other than clear cell

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carcinoma (n=31), hemodialysis (n=17), loss of pathological data (n=13), inflammatory disease (n=3), or bilateral synchronous tumors (n=2). Consequently, the remaining 518 patients with clear cell carcinoma constituted the study cohort. Of the 518 patients 57 underwent partial nephrectomy. This study has approved by the Institutional Review Board.

TNM-C scoring algorithm. The TNM-C score was calculated for each patient according to our previously described scoring algorithm (8). Patients were diagnosed, and the extent of the disease was assessed preoperatively on the basis of clinical findings, computed tomography scans, magnetic resonance imaging, and/or bone scans. All of resected tumors were macroscopically and microscopically examined for pathology. Tumors were staged according to the 2002 TNM criteria proposed by the American Joint Committee on Cancer for pathological staging. Serum CRP was determined preoperatively and expressed in mg/lt. The CRP cut-off point was set at 5.0 mg/lt based on the TNM-C algorithm. The score of each patient was calculated as 2 (if pT3) + 2 (if N1 or N2) + 4 (if M1) +1 (if CRP 5.0 mg/lt or greater) and 0 (otherwise) (Table I).

Table I. *TNM-C scoring algorithm*.

Parameter	Score points
pT classification	
pT1	0
pT2	0
pT3	2
pT4	0
Lymph node involvement	
pNx or pN0	0
pN1	2
pN2	2
Distant metastasis	
M0	0
M1	4
CRP (mg/lt)	
<5.0	0
≥5.0	1

Statistical methods. The primary end-point of the study was cancer-specific survival (CSS). Patients were censored at their date of death. The follow-up period was calculated from the date of surgery to the date of the last visit or cancer-specific death. The CSS rate was estimated using the Kaplan-Meier method and compared by log-rank test. Associations of clinicopathological features with cancer-specific death were evaluated using the Cox proportional hazards regression model. The predictive ability of the TNM-C score was evaluated using Harrell's c-index (9). Interpretation of the c-index is similar to interpretation of the area under a ROC curve. A value of 1.0 indicates that the features in a Cox model perfectly discriminates between patients with different outcomes, while a value of 0.5 indicates that the features contain no predictive information. Statistical analysis was performed using the JMP software (SAS Institute Inc., Cary, NC, USA) and S-Plus software (Mathsoft Data Analysis Product Division, Seattle, WA, USA), with $p<0.05$ considered statistically significant. The c-index was calculated using the Microsoft Excel 2010 software described, as in our previous report (8).

Results

Table II lists the characteristics of patients in the studied cohort. The median follow-up period of the 518 patients was 49 (range=1-241) months at Tsuchiura, 40 (range=1-191) months at Toride, 41 (range=1-223) months at Saitama, and 45 (range=1-241) months for the entire data set. Out of 518 patients, 84 died of ccRCC during the follow-up period. There were no significant differences regarding the patients' characteristics except for cT distribution among the three hospitals. Out of 518 patients, 336 (64.9%) presented with stage T1 disease, 63 (12.1%) with T2 disease, 112 (21.6%) with T3 disease, and 7 (1.4%) with T4 disease. In addition, lymph node involvement was detected in 5 patients (1.0%), and distant metastases were discovered at-nephrectomy in 56 patients (10.8%). Preoperative CRP was elevated in 160 patients (30.9%).

Multivariate analysis revealed that risk factors for CSS are pT3, M1, and CRP (Tsuchiura); pT4, M1, and CRP (Toride); pT3, pT4, M1, and CRP (Saitama); and pT3, pT4, M1, and CRP (entire data set) (Table III). In the present study, regional lymph node involvement was not related to CSS in the multivariate model.

The CSS curves according to the four collapsed groups of patients with scores of 0, 1, and 2; 3 and 4; and 5 or more are shown in Figure 1. Estimated CSS rates for the TNM-C scores are listed in Table IV. Survival curves are clearly stratified and are statistically significant in each of the three hospitals and the entire cohort ($p<0.001$ for all for groups). The five-year CSS rates of patients with scores of 0, and 2, 3 and 4, and 5 or greater were 98.4%, 87.4%, 50.8%, and 21.1%, respectively. The c-indexes for each cohort were 0.85 (Tsuchiura), 0.89 (Toride), 0.83 (Saitama), and 0.85 (entire data set), respectively. The c-indexes using the four collapsed groups were 0.81 (Tsuchiura), 0.87 (Toride), 0.80 (Saitama), and 0.82 (entire data set), which were equivalent to the c-index of the original cohort (0.82) (8). Eliminating CRP from the TNM-C score, the c indexes decreased to 0.76 (Tsuchiura), 0.84 (Toride), 0.76 (Saitama), and 0.75 (entire data set).

Discussion

In the present study, we demonstrated, through external validation, the high predictive accuracy and applicability of the TNM-C score in community hospital cohorts. The TNM-C score uses simple practical parameters which consist solely of TNM classification and preoperative CRP concentration. In the TNM-C score, detailed pathological features such as nuclear grade and tumor necrosis are unnecessary.

Some groups have proposed prognostic models that have high predictive accuracy to predict outcome following

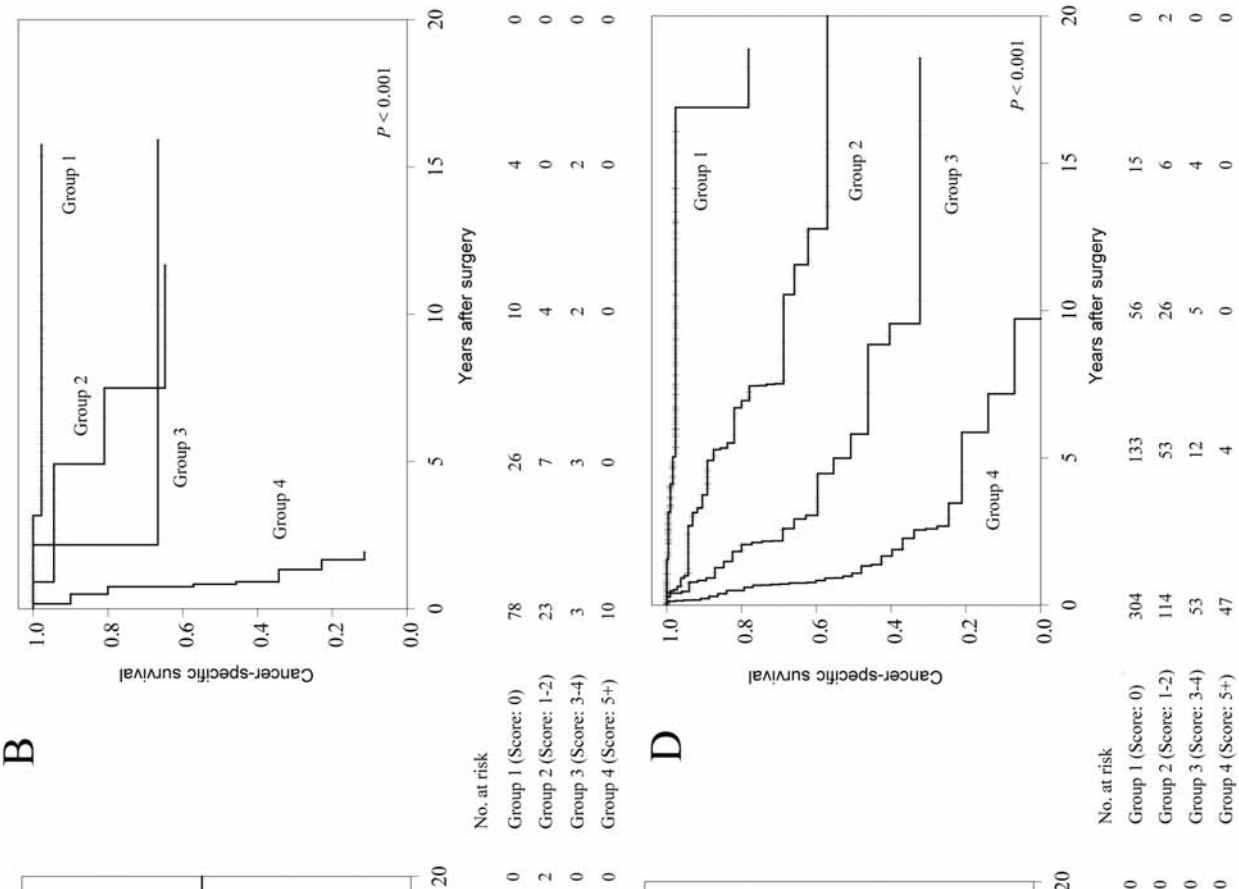

Figure 1. *Cancer-specific survival curves for four groups according to the TNM-C score. A: Tsuchiura Kyodo General Hospital, B: Toride Kyodo General Hospital, C: Saitama Red Cross Hospital and D: Entire data set.*

Table II. *Clinicopathological patient data*.

	Whole date set	Tsuchiura	Toride	Saitama	*p*-Value
Patients (n)	518	195	114	209	
Median age (range)	64 (16-91)	65 (16-91)	64 (31-90)	64 (19-84)	0.9961
Gender (%)					0.3075
Male	340 (65.6)	130 (66.7)	68 (59.6)	142 (67.9)	
Female	178 (34.4)	65 (33.3)	46 (40.4)	67 (32.1)	
pT classification (%)					
pT1	336 (64.9)	133 (68.2)	77 (67.5)	126 (60.3)	<0.001
pT2	63 (12.1)	23 (11.8)	23 (20.2)	17 (8.1)	
pT3	112 (21.6)	38 (19.5)	12 (10.5)	62 (29.7)	
pT4	7 (1.4)	1 (0.5)	2 (1.8)	4 (1.9)	
Lymph node involvement (%)					0.0699
pNx + pN0	513 (99.0)	195 (100.0)	113 (99.1)	205 (98.1)	
pN1 + pN2	5 (1.0)	0 (0.0)	1 (0.9)	4 (1.9)	
Distant metastasis (%)					
M0	462 (89.2)	175 (89.7)	103 (90.4)	184 (88.0)	0.7762
M1	56 (10.8)	20 (10.3)	11 (9.6)	25 (12.0)	
Preoperative CRP (mg/lt) (%)					
<5.0	358 (69.1)	138 (71.8)	84 (73.7)	136 (65.1)	0.2269
≥5.0	160 (30.9)	57 (29.2)	30 (26.3)	73 (34.9)	

Table III. *Multivariate Cox regression analysis of cancer-specific survival*.

	Tsuchiura	Toride	Saitama	Whole data set	
	p-Value	*p*-Value	*p*-Value	HR (95% CI)	*p*-Value
TNM					
pT3*	0.003	0.084	<0.001	3.03 (1.84-5.04)	<0.001
pT4*	0.096	0.002	0.004	14.32 (4.58-37.25)	<0.001
pN1,2†	N.A.	0.610	0.069	2.37 (0.70-6.06)	0.148
M1‡	<0.001	<0.001	<0.001	8.24 (4.78-14.30)	<0.001
CRP (mg/lt)					
≥5.0§	0.010	0.005	0.031	2.83 (1.66-4.91)	<0.001

N.A., Not available; *Reference group is pT1 or 2 tumors; †Reference group is pN0 or pNX tumors; ‡Reference group is M0 group; §Reference group is CRP <5.0 mg/lt.

nephrectomy for RCC patients. These models usually require detailed pathological information such as Fuhrman nuclear grade and histological tumor necrosis. It should be noted, however, that in several reports certain pathological definitions in nuclear grading differ (10-14). Histological tumor necrosis is an independent predictive factor, yet it might not contribute to improving the prognostic model. Moreover, some studies have indicated that tumor necrosis is not actually an independent factor (5, 14).

CRP has been shown to be a significant prognostic factor for RCC (8, 15, 16). Elevated CRP concentration predicts for poor prognosis (8). TNM classification is the most significant prognostication system, and adding CRP to TNM classification could further improve predictive accuracy. With the TNM-C score, survival curves were clearly discriminated and the c-indexes of the score in this validation cohort were equivalent to the c-index of the original cohort (8). The c-indexes of the TNM-C score were improved by adding CRP to the model.

Incorporating CRP into the prognostic algorithm is relatively simple and does not reduce predictive ability. For example, we have reported that the c-index of the TNM-C score is approximately equivalent to the SSIGN score which requires for stage, size, grade, and necrosis (5). In our previous reports, CRP concentration is correlated to aggressive higher-grade tumor characteristics and presence of tumor necrosis (8). CRP can be readily-measured in most

Table IV. *Cancer-specific survival rates by the TNM-C score.*

		% Survival (SE, No. at risk)		
TNM-C score	No. Pts (%)	Year 1	Year 5	Year 10
All scores	518			
0	304	100 (0, 260)	98.4 (0, 133)	97.7 (0, 56)
1	73	98.6 (0, 66)	93.6 (0, 34)	63.9 (0.1, 15)
2	41	89.8(0, 33)	76.5 (0.1, 20)	71.7 (0.1, 12)
3	43	87.2 (0.1, 33)	62.6 (0.1, 12)	39.9 (0.1, 5)
4	10	85.7 (0.1, 7)	0.0	0.0
5	18	46.7 (0.1, 8)	33.3 (0.1, 3)	0.0
6	4	25.0 (0.2, 2)	0.0	0.0
7	23	58.0 (0.1, 12)	0.0	0.0
8	0	No data	No data	No data
9	2	50.0 (0.2, 2)	0.0	0.0
Collapsed score categories				
0	304	100 (0, 260)	98.4 (0, 133)	97.7 (0, 56)
1, 2	114	95.3 (0. 97)	87.4 (0, 53)	68.8 (0, 26)
3, 4	53	87.5 (0, 39)	50.8 (0.1, 12)	32.3 (0.1, 5)
5-	47	50.5 (0.1, 21)	21.1 (0.1, 4)	0.0

SE: Standard error, No.: number, Pts: patients.

facilities using standardized assay kits with high reproducibility. We demonstrated that the TNM-C score could be applied to community hospital cohorts with equivalent predictive accuracy to the referred Center cohort (8). Thus, we believe that the TNM-C score could be applied to assess the prognosis of ccRCC in most hospitals.

In the present study, lymph node involvement was not a significant factor although it was identified as such in a previous report (8). This might be due to the low incidence of lymph node involvement. We have not routinely performed lymph node dissection. The use of routine extended lymphadenectomy in conjunction with radical nephrectomy is considered controversial when there is no preoperative evidence of lymph node involvement (17, 18).

Several limitations must be considered when interpreting our results. Since this study is retrospective in nature, a further prospective study is needed. The external validation was performed using Japanese patient cohorts only, so a wider applicability could be validated by using patients from other regions and ethnic groups. However, on the basis of the high predictive ability and simplicity of the TNM-C score, it could be viewed as widely applicable for Japanese community hospitals, at least.

In conclusion, this study revealed that the TNM-C score has a high prognostic ability, is simple to generate, and can be applied to patients with ccRCC in Japanese community hospitals. Future studies are needed to determine whether the TNM-C score is useful in other regions and ethnic groups.

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