Original Study

Prognostic Significance of C-reactive Protein in Patients With Non-metastatic Papillary Renal Cell Carcinoma: Results from the INternational Marker Consortium for Renal Cancer (INMARC) Cohort

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Abstract

The prognostic value of C-reactive protein was evaluated in patients with non-metastatic papillary renal cell carcinoma undergoing curative surgery using the international multi-institutional cohort. We demonstrated that C-reactive protein was significantly associated with poor recurrence-free survival. C-reactive protein can serve as a useful adjunct biomarker to screen patients with a high risk of recurrence.

Introduction: C-reactive protein is a useful biomarker for screening renal cell carcinoma (RCC); however, its significance in papillary RCC is unclear. We assessed the prognostic effect of serum C-reactive protein levels in patients with surgically treated non-metastatic papillary RCC. **Patients and Methods:** We established an international multi-institutional database (the INternational Marker Consortium for Renal Cancer) of 3799 patients with surgically treated RCC. Among these, data of 400 patients with non-metastatic papillary RCC were analyzed. An elevated pretreatment serum C-reactive protein level was defined as > 10 mg/L. Associations of clinical covariates with recurrence-free survival were investigated. **Results:** Among the patients, 174 were African Americans, 155 were European–Americans, 50 were Asians, and 21 were of other races. Pathological T stages were 1, 2, 3, and 4 in 313, 46, 32, and 3 patients, respectively. The median pretreatment C-reactive protein level was 1.0 mg/L; 48 patients exhibited an elevated C-reactive protein level. During follow-up (median 18 months), 30 patients presented recurrence. The 1-, 3-, and 5-year recurrence-free rates were 95%, 91%, and 87%, respectively. Multivariate analysis revealed a significant association of the elevated pretreatment C-reactive protein level with poor recurrence-free survival (hazard ratio 2.47, 95% confidence interval 1.03-5.48; $P = .043$). The 5-year recurrence-free survival was significantly worse for patients with elevated C-reactive protein levels (67% vs. 90%; $P = .001$). **Conclusions:** C-reactive protein is a significant prognostic factor for patients with non-metastatic papillary RCC and can serve as a useful adjunct biomarker for screening patients with a high risk of recurrence.

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Introduction

Renal cell carcinoma (RCC) includes a wide range of histopathological entities with different biological and clinical behaviors, as described in the 2016 World Health Organization classification.[1]

Abbreviations: ccRCC, clear cell renal cell carcinoma; CRP, C-reactive protein; cT stage, clinical T stage; cN stage, clinical N stage; HR, Hazard ratio; INMARC, INternational Marker Consortium for Renal Cancer; NLR, Neutrophil-to-lymphocyte ratio; pRCC, papillary renal cell carcinoma; pT stage, pathological T stage; pN stage, pathological N stage; RCC, Renal cell carcinoma; RFS, Recurrence-free survival.

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Papillary RCC (pRCC) is the second most common subtype of RCC, accounting for 15% of all RCC cases.[2] While patients with pRCC generally have a more favorable prognosis than those with clear cell RCC (ccRCC), pRCC reportedly has a low T stage and may have a poor prognosis compared with ccRCC in similar stages of more advanced or metastatic cancers—the difference remains controversial.[3,4] However, evidence regarding the clinicopathological features including serum parameters predictive of the prognostic outcome in patients with pRCC is limited.[5] Moreover, several RCC prognostic models represented by the TNM classification have mainly been established for either ccRCC alone or all RCC subtypes together.[6] Other clinical and pathological factors of RCC prognosis have also been identified, including age, tumor necrosis factor, Fuhrman grade, performance status, and histological subtype; many of them have been investigated in all RCC subtypes, particularly ccRCC.

Recent advances in understanding the etiology of cancer have revealed that the complex interactions between tumor and host inflammatory responses affect disease progression.[7,8] C-reactive protein (CRP) is a nonspecific inflammatory acute-phase protein and frequently increases in the serum of patients with cancer. CRP is also recognized as a prognostic factor in patients with metastatic and localized RCC.[9-18] Although pRCC has been recognized to be associated with better survival outcomes than ccRCC, metastasis can still occur, ultimately increasing mortality.[3,4] As the information available regarding the prognostic factors for pRCC is limited, identifying such factors, including serum parameters, could help improve our understanding of the mechanism of disease progression and treatment outcomes. To date, the prognostic significance of clinical serum parameters and the relationship between CRP and pRCC prognosis have not been well investigated.

In the present study, we aimed to assess the prognostic effect of CRP measured preoperatively in patients with non-metastatic pRCC receiving surgical treatment, using an international multi-institutional dataset.

Patients and Methods

Patients

This study was reviewed and approved by Tokyo Medical and Dental University (M2017-177), and written informed consent was obtained from all participants. We established an international multi-institutional cohort (the INternational Marker Consortium for Renal Cancer [INMARC)]) of patients with surgically treated RCC—3,799 patients with RCC who underwent radical or partial nephrectomy between 2000 and 2017. The centers that participated in this study were Tokyo Medical and Dental University, Japan; University of California, San Diego, CA, USA; and Emory University, Atlanta, GA, USA. Patient and tumor characteristics, including relevant demographic data and pathological findings, were obtained based on the review of clinical and pathological records to develop the database. Tumors were staged according to the 7th edition of the TNM Staging System for Renal Tumor Classification proposed by the American Joint Committee on Cancer.[19] Tumors were also evaluated using Fuhrman nuclear grade criteria.[20] In the established database, we included data of patients with pRCC and excluded patients with lymph node or distant metastasis. We also excluded patients with bilateral tumors. Finally, 400 patients with non-metastatic pRCC were identified and retrospectively analyzed in this study. Patients were regularly followed up according to protocols established at each institution. The follow-up period began at the date of surgery and ended at the final follow-up.

Clinical and Laboratory Assessments

We assessed clinical and laboratory variables, including age, sex, race, laterality, type of surgery (radical nephrectomy or partial nephrectomy), pathologic T (pT) stage, clinical T (cT) stage, pathological N (pN) stage, Fuhrman grade, neutrophil-to-lymphocyte ratio (NLR), and serum CRP. The NLR and serum CRP levels were evaluated as a part of a preoperative laboratory study. An elevated pretreatment serum CRP was defined as a serum CRP level of $>$ 10 mg/L.[17] Accordingly, the study cohort was divided into 2 groups with or without elevated serum CRP ($>$ 10 and $\leq$ 10 mg/L, respectively).

Statistical Analysis

The primary endpoint of this study was recurrence-free survival (RFS), which was estimated using the Kaplan–Meier method. The study cohort was divided into 2 groups ($>$ 10 and $\leq$ 10 mg/L pretreatment serum CRP) for descriptive analyses. To compare the two groups, Mann–Whitney U and Pearson's chi-square tests for continuous and categorical variables, respectively, were conducted. Associations of RFS with clinical covariates were determined using the Cox proportional hazards model, with $P < .05$ considered to indicate significance for all analyses. The continuous variables were dichotomized using the median as the cut-off value. All analyses were performed using JMP version 10.0.2 (SAS Institute, Cary, NC, USA).

Results

Patient and tumor characteristics are summarized in Table 1; the median follow-up period was 18 months. Four hundred patients who underwent radical nephrectomy or partial nephrectomy for pRCC were analyzed. The median age was 61 years, and the majority of patients were males. Among the 400 patients assessed, African Americans formed the highest proportion, followed by European–Americans, Asians, and patients of other races. The incidence of left- and right-sided disease and the distribution of patients who underwent radical and partial nephrectomy were almost equal. The majority of patients were in cT stage 1, pT stage I, and Fuhrman grades 2 or 3.

The median (interquartile range [IQR]) CRP level was 1.0 (0-4.1) mg/L. The CRP level was elevated in 48 patients (12%). An elevation in the pretreatment CRP level was significantly associated with race, cT stage, and pT stage; however, it was not associated with age, the proportion of males, laterality, type of surgery, tumor size, NLR, pN stage, and Fuhrman grade (Table 1).

During the follow-up, 30 patients (8%) presented recurrence. The RFS rate for the entire cohort was 95% after 1 year, 91% after 3 years, and 87% after 5 years (Figure 1). Among the 48 patients with an elevated serum CRP level, 9 (19%) patients presented

Table 1 Patient and Tumor Characteristics

Variable	CRP ≤10 mg/L		CRP >10 mg/L		*P*
No. of patients	**352**	**(88.0%)**	**48**	**(12.0%)**	
Age (years, median [IQR])	61	(52-69)	58	(53-66)	.399
Sex					
Male	252	(71.6%)	29	(60.4%)	.112
Female	100	(28.4%)	19	(39.6%)	
Race					
African–American	144	(40.9%)	30	(62.5%)	.036
European–American	141	(40.1%)	14	(29.2%)	
Asian	47	(13.3%)	3	(6.2%)	
Others	20	(5.7%)	1	(2.1%)	
Laterality					
Left	168	(47.7%)	26	(54.2%)	.674
Right	178	(50.6%)	21	(43.8%)	
Unknown	6	(1.7%)	1	(2.1%)	
Type of surgery					
Radical nephrectomy	180	(51.1%)	25	(52.1%)	.902
Partial nephrectomy	172	(48.9%)	23	(47.9%)	
cT stage					
cT1	297	(84.4%)	32	(66.7%)	.003
cT2	41	(11.7%)	10	(20.8%)	
cT3	5	(1.4%)	4	(8.3%)	
Unknown	9	(2.6%)	2	(4.2%)	
Tumor size (cm, median [IQR])	3.5	(2.0-5.5)	4.0	(2.4-7.3)	.076
CRP (mg/L, median [IQR])	0.7	(0-2.7)	21	(15-33)	<.001
NLR (median [IQR])	2.5	(1.6-3.6)	2.7	(1.9-4.1)	.673
pT stage					
pT1	279	(79.3%)	34	(70.8%)	.030
pT2	43	(12.2%)	3	(6.3%)	
pT3	24	(6.8%)	8	(16.7%)	
pT4	2	(0.6%)	1	(2.1%)	
Unknown	4	(1.1%)	2	(4.2%)	
pN stage					
pN0	268	(76.8%)	38	(79.2%)	.774
pN1	2	(0.6%)	0	(0%)	
pN2	3	(0.9%)	1	(2.1%)	
pNX	76	(21.8%)	9	(18.8%)	
Unknown	3	(0.9%)	0	(0%)	
Fuhrman grade					
Grade 1	22	(6.3%)	2	(4.2%)	.927
Grade 2	152	(43.2%)	19	(39.6%)	
Grade 3	150	(42.6%)	22	(45.8%)	
Grade 4	10	(2.8%)	2	(4.2%)	
Unknown	18	(5.1%)	3	(6.3%)	

Abbreviations: CRP = C-reactive protein; cT = clinical T; IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; pT = pathological T; pN = pathological N.
Mann–Whitney U and Pearson's chi-square tests were conducted for continuous and categorical variables, respectively.

Figure 1 Kaplan–Meier curve predicting recurrence-free survival of patients with non-metastatic papillary renal cell carcinoma in an international multi-institutional cohort.

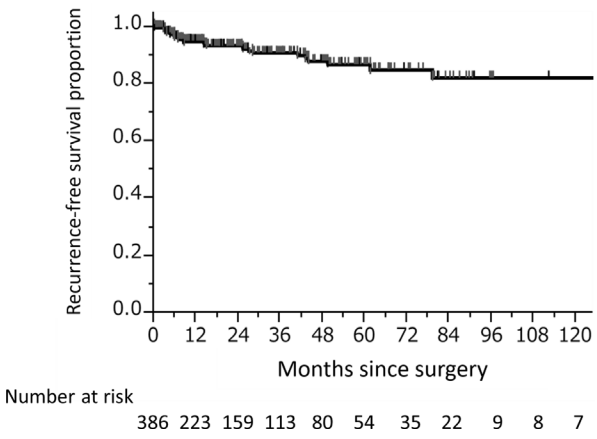
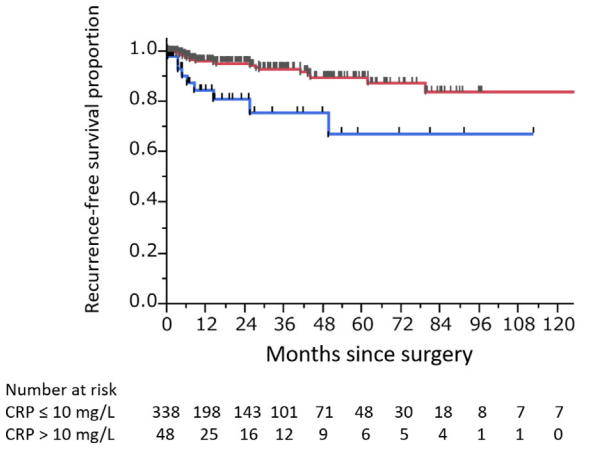


Figure 2 Kaplan–Meier analysis of recurrence-free survival stratified by the pretreatment C-reactive protein (CRP) level (red line for CRP ≤ 10 mg/L and blue line for CRP > 10 mg/L).



recurrence. In contrast, 21 (6%) of the 338 patients without an elevated serum CRP level presented recurrence. An elevation in the pretreatment serum CRP level was significantly associated with recurrence ($P = .002$). The 5-year RFS rate of patients with an elevated serum CRP level (67%) was significantly worse than that of patients without an elevated serum CRP level (90%) (Figure 2, $P = .0012$).

In the patients with elevated serum CRP levels, 4 (13%), 1 (10%), and 3 (75%) patients experienced recurrences in the cT1, cT2, and cT3 groups, respectively. In contrast, recurrence was observed in 13 (5%), 3 (7%), and 4 (80%) patients with cT1, cT2, and cT3, respectively, in those without elevated serum CRP levels. In the sub-analysis of cT1 patients, the 5-year RFS rate was 70% and 92% in the patients with and without elevated serum CRP levels, respectively (Supplementary Figure 1, $P = .0338$).

Table 2 shows the results of the multivariate analysis for independent risk factors associated with disease recurrence. The Cox proportional hazards model was used to elucidate risk factors for disease recurrence, including age (> 61 vs. ≤ 61 years), sex (male vs. female), race (African–American vs. non-African–American), type of surgery (radical nephrectomy vs. partial nephrectomy), serum CRP (> 10 vs. ≤ 10 mg/L), NLR (> 2.5 vs. ≤ 2.5), pT stage (pT3–T4 vs. pT1–T2), pN stage (pN1-N2 vs. pNX-N0), and Fuhrman grade (3-4 vs. 1-2). Among these factors, the pretreatment elevated serum CRP level was significantly associated with a poor RFS. pT

Table 2 Cox Regression Analysis of Risk Factors for Recurrence

Variable	Univariate	Multivariate	
	P	HR (95% CI)	*P*
Age > 61 (reference ≤ 61)[a]	.931		
Male sex (reference female)	.178		
African–Americans (reference non-African–Americans)	.482		
Radical nephrectomy (reference partial nephrectomy)	.137		
CRP > 10 mg/L (reference CRP ≤ 10 mg/L)	.006	2.47 (1.03-5.48)	.043
NLR > 2.5 (reference NLR ≤ 2.5) [a]	.289		
pT stage group 3–4 (reference pT1–2)	<.001	4.54 (2.00-9.83)	<.001
pN stage group 1-2 (reference pN)	.053		
Fuhrman grade 3–4 (reference Fuhrman grade 1–2)	.626		

CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; pT = pathological T; pN = pathological N.
[a] Continuous variables were dichotomized using the median as the cut-off value.

stages 3-4 also emerged as an independent risk factor for disease recurrence.

Discussion

This study included a substantial number of patients with pRCC derived from an international multi-institutional RCC database. An analysis of data from this database has indicated that the serum CRP level is associated with postoperative renal dysfunction and non-cancer mortality.[21] In the present study, serum CRP level, and pT stage were identified as significant prognostic factors of RFS in patients with non-metastatic pRCC. This result supports the importance of pT stage as an independent prognostic factor.[22] Furthermore, the elevation in the serum CRP level (> 10 mg/L), as a preoperative clinical factor, was significantly associated with a worse RFS. These results were also confirmed when CRP was examined as a continuous value. These results are consistent with those of previous studies on ccRCC highlighting the serum CRP as an important factor that reflects malignant potential.[9,17] These results also suggest that the presence of a host inflammatory reaction, as indicated by an elevated CRP level, reflects tumor aggressiveness and, consequently, a worse survival outcome.

The mechanism by which systemic inflammatory responses, such as an elevated serum CRP, affect cancer prognosis has not been fully elucidated. However, the release of inflammatory cytokines and growth factors is known to be a part of the systemic inflammatory response to tumors. They also play a significant role in the catabolism of the metabolic substrates of host cells and stimulate tumor growth.[10,23,24] The cytokines that strongly induce CRP production in the liver are interleukin-1, tumor necrosis factor, and interleukin-6. Interleukin-6 production in renal tumors has been shown in studies on RCC cell lines and analysis of surgical specimens of renal cancer; it also promotes renal tumor growth.[25,26] Thus, there might be an association between the systemic inflammatory response and local RCC aggression. In vitro studies have also shown that anti-inflammatory factors, glucocorticoids, exert an anti-angiogenic activity by downregulating the vascular endothelial growth factor, which is overexpressed in patients with RCC and is known to be involved in the proliferation of RCC cells.[27]

Previous studies have reported that CRP is a prognostic factor for ccRCC.[9,17] The present study showed that this also applies to pRCC. However, the cutoff levels of CRP used in previous studies are different.[9,28] Although we used the cutoff level considered in previous studies, there is no established ideal cutoff value.[28] The reason for these deviations may be that the baseline CRP level differs depending on the histological type. As a future prospect, the effect of the variation in CRP cut-off should be systematically investigated, including other histological types.

A subgroup analysis was performed for each clinical stage, and CRP was a significant prognostic factor in only the clinical T1 stage group. One of the reasons for this might be that the number of cases in each group was too small when divided into subgroups. On the contrary, the multivariate analysis showed that CRP contributes to prognosis prediction independent of the stage. This is a limitation of this study, and as a prospect, the prognostic factors in each clinical stage should be investigated by increasing the number of patients.

NLR is an inflammatory marker; it has also been reported to be a prognostic factor for RCC.[29] On the contrary, it has been reported that CRP and NLR do not always show a correlation. Increasing the number of patients may prove the utility of NLR in this respect.

We acknowledge that there are several other limitations to this study. First, the median follow-up period was limited to 18 months. Second, the difference between pRCC subtypes 1 and 2 was not examined in this cohort. Data on the pRCC subtype were not available for a moderate number of patients in our database. Recent reports have stated that the classification of types 1 and 2 has poor reproducibility among pathologists and might not be recommended in the future.[30] Overall, CRP, which is a preoperative marker, is meaningful. Finally, the lack of a central review of clinical and pathological data, including the surgical procedure used for partial nephrectomy, is another limitation of this study. However, such an analysis was beyond the scope and feasibility of this type of retrospective study, involving more than 3000 patients from several locations and countries.

Conclusions

This study, using data from an international multi-institutional database, showed that the elevation in the serum CRP level is associated with a poor prognosis for patients with non-metastatic pRCC. Serum CRP measurement is a simple and low-cost test, and its reproducibility and reliability are high in pRCC clinical practice. Thus, assessing the serum CRP level can be a useful method to screen patients with pRCC at a high risk of disease recurrence. Future research on new treatments for RCC may require monitoring of CRP to assess the response. Moreover, assessing the pretreatment CRP level might facilitate the planning of follow-ups for patients with non-metastatic pRCC.

Clinical Practice Points

- CRP is a valuable biomarker for RCC; however, its significance in pRCC is unclear.
- We demonstrated that CRP was significantly associated with poor RFS in patients with non-metastatic pRCC undergoing curative surgery using the international multi-institutional cohort.
- Assessing the serum CRP level can be a useful method to screen patients with pRCC at a high risk of disease recurrence. Our results raise the possibility of a CRP-based approach for managing patients with pRCC, including risk stratification and participation in clinical trials.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.03.004.

CRediT authorship contribution statement

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