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C-reactive protein-albumin ratio as a prognostic factor in renal cell carcinoma – A data from multi-institutional study in Japan

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Abstract

Introduction: The C-reactive protein to albumin ratio (CAR) has been shown to provide prognostic information in several cancers. The objective in the study is to examine the prognostic value of CAR in patients with RCC who underwent nephrectomy.

Material and Methods: The record data from multi-institutional study of 1,028 patients was analyzed in the study. The cut-off value of the CAR was defined by receive operating characteristic (ROC) analysis. Overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) were evaluated, and univariate and multivariate analyses were conducted to assess the predictive value of the variables including CAR.

Result: The optimal cut-off value of 0.073 in CAR was defined according to the ROC analysis. The AUC in CAR for CSS was greater than that of NLR and PLR, and that for RFS was also greater than GPS and mGPS. Multivariate analysis demonstrated that the CAR was an independent prognostic factor for OS ($P < 0.001$), CSS ($P < 0.001$) in total cohort and RFS ($P = 0.029$) in nonmetastatic cohort.

Conclusion: The findings of the present study suggested that the preoperative CAR is an independent prognostic indicator of OS, CSS and RFS for patients with RCC. Since CAR can be assessed prior to surgery, clinicians should this take into account for the treatment decision making.

Key Words: Renal cell carcinoma; CRP/Alb ratio; Inflammation-based prognostic score; NLR; Systemic inflammatory response

1. Introduction

Renal cell carcinoma (RCC) is the most common kidney cancer, and expected numbers in United States accounts for 65,340 of new cases and 14,970 of deaths in 2018 [1]. There has been accumulating evidence that systemic inflammatory and nutrition status (SINS) are associated with clinical outcomes in the treatment for RCC [2–5]. We previously reported that lower body mass index (BMI) is associated with poor prognosis in localized RCC treated with curative nephrectomy [4]. By now, increasing evidence has suggested the involvement of systemic nutritional and inflammation status in cancer progression. Serum C-reactive protein (CRP) and albumin (Alb) level are indicators of poor nutritional status as well as chronic inflammation in cancer patients [6–9]. In addition, inflammation-based prognostic scores including the neutrophil lymphocyte ratio (NLR),

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derived neutrophil-to-lymphocyte ratio (dNLR), platelet lymphocyte ratio (PLR), Glasgow prognostic score (GPS), and modified GPS (mGPS) have been reported to show prognostic value in a number of type of cancers, including RCC [10–16]. Recent studies have demonstrated the CRP to Alb ratio (CAR) is an independent prognostic factor in hepatocellular cancer (HCC), gastric cancer (GC), small-cell lung cancer (SCLC) [17–19]. Chen et al. and Guo et al. reported that the elevation of CAR is associated with worse prognosis in patients with RCC [20,21]. In the present study, we assessed the clinical impact of CAR in RCC patients treated with nephrectomy in multi-institutional Japanese cohort.

2. Materials and methods

2.1. Patients

Two RCC databases from Tokyo Medical University and Osaka Medical College were combined. There were 1,028 consecutive patients assigned in the study from 1990 to 2015. Following patients were excluded from the study (Fig. 1), i.e., 49 patients who did not undergo nephrectomy, 219 patients missing any clinicopathological information and 61 patients with insufficient follow-up (less than 12 months). Accordingly, 699 patients were included in the analysis. The study was performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki [22]. Written informed consent was obtained from all participants for the study registry.

2.2. Clinicopathological characteristics

Clinical stage in each patient was evaluated by computer tomography (CT), magnetic resonance imaging (MRI), ultrasound, and chest-X ray, and other patient information including performance status (Eastern Cooperative Oncology Group, ECOG-PS) were preoperatively recorded. Pathological review including Fuhrman nuclear grade [23] was examined in all patients as well as the 7th TNM classification of the UICC and AJCC guidelines of renal tumors. Routine laboratory measurements including CRP and Alb were determined preoperatively (1–2 weeks before the surgery). The CAR was calculated dividing the serum CRP (mg/l) level by the serum Alb (g/l) level. The UISS score was assigned as previously described [24], stratifying patients into low-, intermediate- or high-risk groups according to the combination of tumor stage, Fuhrman grade, and ECOG-PS.

2.3. Follow-up

Follow-up schedules were applied referring to the NCCN Clinical Practice Guidelines. Follow-up CT and Chest X-ray were performed to detect any findings suspected to disease progression every three months in the first 2 year. Thereafter, patients were followed up every 6 months. Duration of the follow-up was calculated from the day of surgery to the day of death or the last visit.

2.4. Statistical analysis

OS and CSS after nephrectomy were evaluated in all patients ($n = 699$). RFS was calculated from the date of surgery to the date of disease recurrence or metastasis or the last follow-up in M0 RCC patients who underwent nephrectomy ($n = 627$). The optimal cut-off points for the inflammation-based factors including CAR were determined by receive operating characteristic (ROC) analysis and the

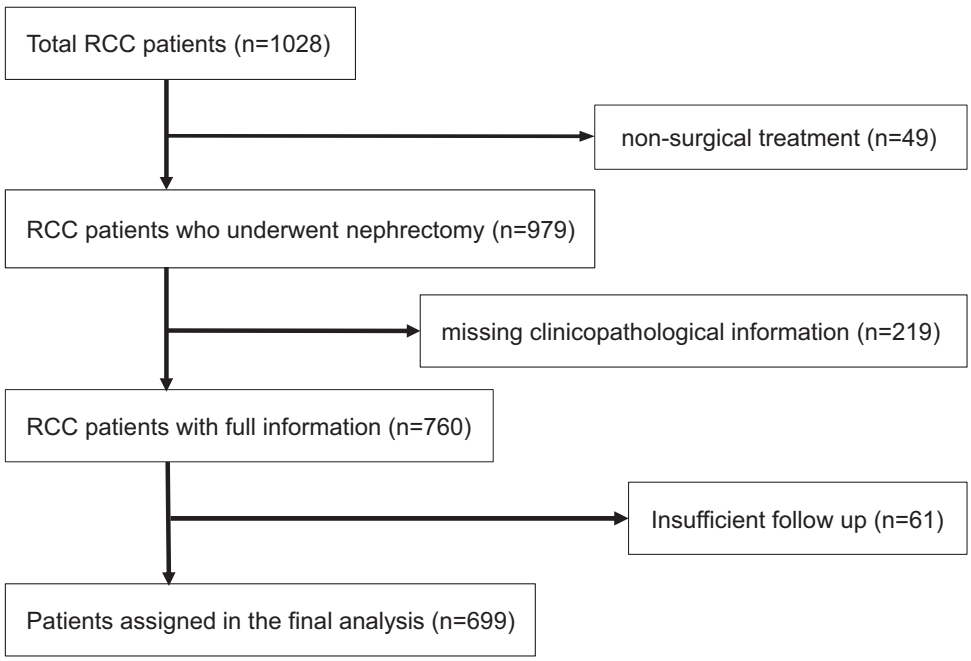

Fig. 1. Flowchart of the patient selection process.

areas under the curve (AUC). Clinicopathological findings in the analysis included patient age, sex, BMI, ECOG-PS, TNM classification, histology type, tumor size, nuclear grade, preoperative NLR, PLR, GPS, mGPS and CAR. Distribution of each factor was evaluated by contingency table with Chi-square analysis. Kolmogorov-Smirnov normality was performed to check normal distribution in continuous variables followed by conducting Student's *t* test or one-way ANOVA was examined to assess difference between the variables. For variables with non-normal distribution, Wilcoxon or Kruskal-Wallis test was performed to assess the difference. A Kaplan-Meier analysis was carried out to estimate survival free ratio, and log-rank test was performed to compare the difference between assigned patient groups. On univariate and multivariate analysis, Cox proportional-hazard regression models, stratified by the factors described above, were used to estimate crude hazard ratios (HR) followed by calculating covariate-adjusted HR. On multivariate analysis, variables that exhibited a significant association in univariate analysis were examined. All statistical tests were two sided, with $P < 0.05$ considered to indicate statistical significance. All analyses were done using JMP 13 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Cut-off value of the parameters

Based on the AUC for predicting OS in the ROC analysis, the Youden index, which maximizes the vertical distance from the reference line, offered the optimal cut-off value of 0.073 in CAR, as well as 3.38 in NLR and 192 in PLR, respectively (Fig. 2). With this cut-off value, the sensitivity and specificity of CAR were 80.9 % and 70.8 %, respectively.

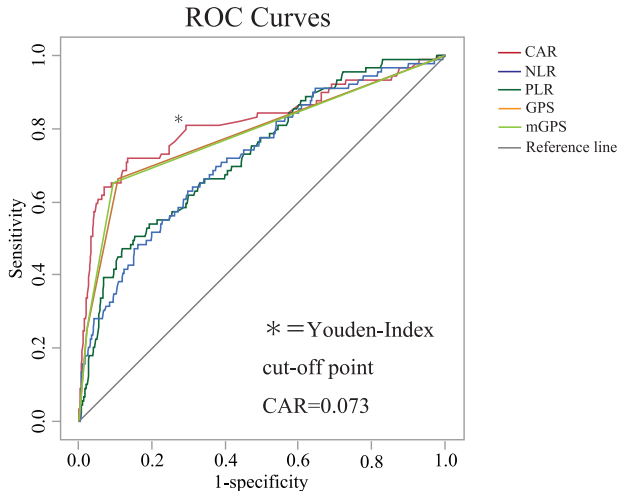

Fig. 2. The ROC curves of inflammation-based prognostic scores including the CAR, NLR, PLR, GPS and mGPS. The Youden-index was applied to determine the optimal cut-off value. (CAR, C-reactive protein to albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil count to lymphocyte count ratio; PLR, platelet lymphocyte ratio; ROC, receive operating characteristic)

Accordingly, 449 (64.2%) patients with CAR ≤0.073 were assigned in low CAR group, and patients with CAR > 0.073 ($n = 250$: 35.8%) were classified into high CAR group.

3.2. Characteristics in all 699 patients

Clinicopathological characteristics in all 699 patients are shown in Table 1. There were 522 (83.3%) and 105 patients (16.7%) who underwent radical and partial nephrectomy. The median follow-up time from nephrectomy was 73 months. A total of 169 (24.2%) patients were died with 33 months of median OS. Kaplan-Meier estimates showed 81.4% and 85.9% of 5-year overall and cancer specific survival rate in all 699 patients, respectively. The distribution of characteristics was significantly varied in ECOG-PS, T classification, N classification, metastasis, tumor size, nuclear grade, UISS, NLR, and PLR, according to CAR. Five years OS and CSS rates for patients in low CAR group were 92.1% and 95.8%, and those in patients with high CAR group were 61.4% and 67.1%, respectively (Fig. 3a, 3b), illustrating a significant difference of prognosis in CAR for RCC patients (OS: $P < 0.001$, CSS: $P < 0.001$ in log-rank test).

To further elucidate prognostic value of the CAR, we stratified the cohort into two groups according to the presence of metastasis at the time of nephrectomy. As expected, the patients with metastatic RCC ($n = 72$) had significantly shorter survivals (5 years OS rate: 19.8%, 5 years CSS rate: 20.0%) compared to the M0 patients (5 years OS rate: 88.0%, 5 years CSS rate: 93.0%). Clinicopathological characteristics were significantly varied between these 2 groups in ECOG-PS, T classification, N classification, tumor size, nuclear grade, UISS, NLR, and PLR, as well as CAR (429/198: M0 patient, 20/52: M1 group: $P < 0.001$). In M0 patients group ($n = 627$), the higher CAR was related with shorter OS (log-rank test: $P < 0.001$) and CSS (log-rank test: $P < 0.001$) (Fig. 3c, 3d). Of note, in M1 patients group ($n = 72$), the higher CAR also exhibited an association with shorter OS (log-rank test: $P = 0.013$) (Fig. 3e). Furthermore, we assessed a correlation between the CAR and recurrence in the patients with M0 RCC, 135 patients (21.5%) of which relapsed with 30 months of median RFS. Kaplan-Meier estimates demonstrated that the higher CAR was significantly associated with shorter RFS (log-rank test: $P < 0.001$) (Fig. 3f).

3.3. Cox regression analysis for OS, CSS in all patients (n = 699), and RFS in patients with M0 RCC (n = 627)

We performed univariate and multivariate analysis to assess predictive value for OS and CSS in all patients (Table 2). Univariate analysis identified several variables significantly associated with OS including age (HR: 1.64, 95% confidence interval [CI]: 1.20−2.24, $P = 0.002$), BMI (HR: 1.58, 95%CI: 1.16−2.13, $P = 0.003$), ECOG-PS (HR: 5.84, 95%CI: 4.20−8.04, $P < 0.001$), T classification (HR: 5.75, 95%CI: 4.23−7.79, $P < 0.001$), N classification (HR:

Table 1
Baseline characteristics of total patients ($n = 699$) according to CAR and the presence of metastasis

Characteristics		CAR			Metastasis		
	Patients ($n = 699$)	<0.073 ($n = 449$)	>0.073 ($n = 250$)	P value	Negative ($n = 627$)	Positive ($n = 72$)	P value
Age (years) (mean ± SD)	61.9 ± 11.7	61.3 ± 12.0	62.9 ± 11.11	ns	61.7 ± 11.9	63.9 ± 9.90	ns
Sex (male/female)	500/199	322/127	178/72	ns	451/176	49/23	ns
BMI (<22.4/>22.4)	277/422	171/278	106/144	ns	379/248	43/29	ns
ECOG-PS (0/>1)	600/99	411/38	189/61	<0.001*	570/57	30/42	<0.001*
T classification (1-2/3-4)	564/135	397/52	167/83	<0.001*	540/87	24/48	<0.001*
N classification (0/1)	661/38	436/13	225/25	<0.001*	611/16	50/22	<0.001*
Histology type (clear/papillary/ chromophobe/others)	627/33/16/23	408/20/12/9	219/13/4/14	ns	562/29/16/20	65/4/0/3	ns
Tumor size (cm) (mean ± SD)	4.9 ± 2.6	4.2 ± 2.2	6.4 ± 3.1	<0.001*	4.7 ± 2.6	7.2 ± 2.7	<0.001*
Nuclear grade (1-2/3-4)	552/147	397/52	155/95	<0.001*	518/109	34/38	<0.001*
Metastasis at diagnosis (-/+)	627/72	429/20	198/52	<0.001*	−	−	−
UISS (Low/intermediate-high)	398/301	314/135	84/166	<0.001*	394/233	4/68	<0.001*
NLR (<3.38/>3.38)	538/161	367/82	171/79	<0.001*	503/124	35/37	<0.001*
PLR (<192/>192)	497/202	342/107	155/95	<0.001*	464/163	33/39	<0.001*
CAR (<0.073/>0.073)	449/250	−	−	−	429/198	20/52	<0.001*
5-year overall survival rate (%)	81.4	92.1	61.4	−	88.0	19.8	−

BMI, body mass index; CAR, C-reactive protein to albumin ratio; ECOG-PS, eastern cooperative oncology group-performance status; NLR, neutrophil count to lymphocyte count ratio; ns, nonsignificant; PLR, platelet lymphocyte ratio; SD, standard deviation; UISS, UCLA integrated staging system; *$P < 0.05$.

5.97, 95%CI: 3.92−8.79, $P < 0.001$), tumor size (HR:3.49, 95%CI: 2.46−5.08, $P < 0.001$), nuclear grade (HR: 4.25, 95%CI: 3.13−5.77, $P < 0.001$), metastasis (HR: 12.84, 95%CI: 9.09−17.97, $P < 0.001$), UISS (HR: 6.15, 95%CI: 4.33−8.91, $P < 0.001$), NLR (HR: 2.74, 95%CI: 2.00 −3.73, $P < 0.001$), PLR (HR: 2.43, 95%CI: 1.79−3.30, $P < 0.001$), and CAR (HR: 4.29, 95%CI: 3.15−5.92, $P < 0.001$). On multivariate analysis adjusting with those variables that exhibited a significant association in univariate analysis, 5 variables including ECOG-PS (HR: 2.04, 95%CI: 1.38−3.01, $P < 0.001$), T classification (HR: 1.87, 95%CI: 1.27−2.77, $P = 0.002$), metastasis at diagnosis (HR: 3.63, 95%CI: 2.37−5.55, $P < 0.001$), UISS (HR: 1.67, 95%CI: 1.02−2.76, $P = 0.042$), and CAR (HR: 2.33, 95%CI: 1.65−3.33, $P < 0.001$) still remained as significant predictors for OS.

We next examined the predictive value of those variables for CSS. Multivariate analysis for CSS adjusting with variables, which were significantly associated in univariate analysis including BMI (HR: 1.67, 95%CI: 1.17−2.38, $P = 0.005$), sex (HR: 1.56, 95%CI: 1.08−2.24, $P = 0.012$), ECOG-PS (HR: 7.97, 95%CI: 5.50−11.46, $P < 0.001$), T classification (HR: 8.94, 95%CI: 6.25−12.89, $P < 0.001$), N classification (HR: 7.76, 95%CI: 4.96−11.73, $P < 0.001$), tumor size (HR: 11.51, 95%CI: 6.35−23.48, $P < 0.001$), nuclear grade (HR: 6.86, 95%CI: 4.27−11.05, $P < 0.001$), metastasis at diagnosis (HR: 20.64, 95%CI: 14.05 −30.25, $P < 0.001$), UISS (HR: 15.55, 95%CI: 9.09 −29.03, $P < 0.001$), NLR (HR: 3.42, 95%CI: 2.38−4.88, $P < 0.001$), PLR (HR: 2.98, 95%CI: 2.09−4.25, $P < 0.001$), and CAR (HR: 5.80, 95%CI: 3.97−8.65, $P < 0.001$), revealed six independent predictors for CSS in RCC patients who underwent nephrectomy including ECOG-PS (HR: 2.03, 95%CI: 1.31−3.14, $P = 0.002$), T classification (HR: 1.96, 95%CI: 1.84−3.00, $P = 0.002$), tumor size (HR: 2.50, 95%CI: 1.21−5.18, $P = 0.014$), metastasis at diagnosis (HR: 4.55, 95%CI: 2.85−7.29, $P < 0.001$), UISS (HR: 2.65, 95%CI: 1.31−5.34, $P = 0.007$), and CAR (HR: 2.51, 95%CI: 1.64−3.84, $P < 0.001$).

Next, we assessed predictive value for RFS in patients with M0 RCC at the time of nephrectomy. Univariate analysis identified several variables significantly associated with RFS including ECOG-PS (HR: 2.20, 95%CI: 1.31−3.49, $P = 0.004$), T classification (HR: 4.80, 95%CI: 3.33−6.85, $P < 0.001$), tumor size (HR:3.83, 95%CI: 2.60−5.79, $P < 0.001$), nuclear grade (HR: 3.49, 95%CI: 2.43−4.95, $P < 0.001$), UISS (HR: 3.48, 95%CI: 2.47−4.94, $P < 0.001$), NLR (HR: 2.35, 95%CI: 1.62−3.37, $P < 0.001$), PLR (HR: 2.23, 95%CI: 1.57−3.15, $P < 0.001$), and CAR (HR: 2.58, 95%CI: 1.84−3.61, $P < 0.001$). On multivariate analysis adjusting with those variables that exhibited significant associations in univariate analysis, 6 variables including BMI (HR: 1.53, 95%CI: 1.08−2.17, $P = 0.017$), T classification (HR: 2.54, 95%CI: 1.60−4.07, $P < 0.001$), tumor size (HR:2.29, 95%CI: 1.47−3.64, $P < 0.001$), nuclear grade (HR: 1.77, 95%CI: 1.12−2.81, $P = 0.015$), NLR (HR: 1.68, 95%CI: 1.11−2.51, $P = 0.012$), and CAR (HR: 1.51, 95%CI: 1.04−2.19, $P = 0.029$) still remained as significant predictors for RFS (Table 3).

3.4. Predicting value of CAR comparing to the other variables

To compare the predictive value between CAR, we assessed AUC value in NLR, PLR, GPS and mGPS, for cancer-specific lethality in all RCC patients and relapse in

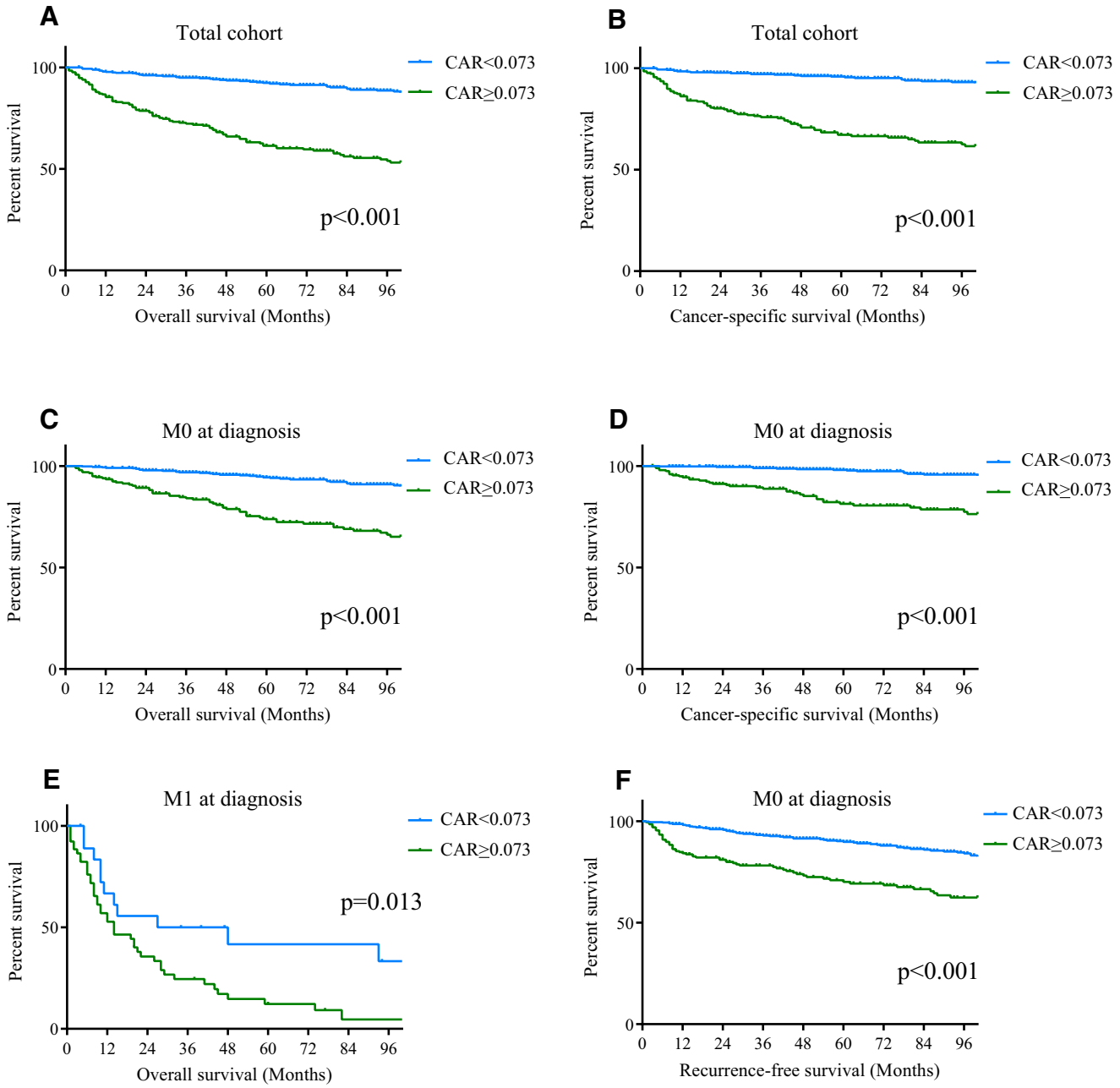

Fig. 3. Kaplan-Meier curves according to CAR (<0.073 and ≥0.073) of (A) Overall survival and (B) cancer-specific survival in all 699 patients, of (C) overall survival and (D) cancer-specific survival in M0 patients group (n = 627), of (E) overall survival in M1 patients group (n = 72), and of (F) recurrence-free survival in M0 patients group (n = 627). (CAR, C-reactive protein to albumin ratio)

M0 RCC patients (Table 4). The AUC in CAR for the CSS at period of 5 years was 0.82 (95%CI: 0.75−0.87), which was greater than that of NLR (AUC=0.73, 95%CI: 0.67−0.78, P = 0.027) and PLR (AUC = 0.72, 95%CI: 0.66−0.78, P = 0.013), and comparable to GPS (AUC = 0.78, 95%CI: 0.73−0.83, P = 0.066), mGPS (AUC = 0.78, 95%CI: 0.73−0.83, P = 0.068) and UISS (AUC = 0.87, 95%CI: 0.83−0.90, P = 0.088). In addition, the AUC value of CAR for the RFS at period of 5 years was 0.69 (95%CI: 0.62−0.75), which was also greater than that of GPS (AUC = 0.64, 95%CI: 0.59−0.69, P = 0.029), and mGPS (AUC = 0.64, 95%CI: 0.59−0.69, P = 0.031), and comparable to that of NLR (AUC = 0.66, 95%CI: 0.59−0.71, P = 0.413), PLR (AUC = 0.65, 95%CI: 0.58−0.71, P = 0.317), and UISS (AUC = 0.70, 95%CI: 0.64−0.75, P = 0.841). These results indicated that the CAR is a durable indicator for predicting both the lethality and recurrent progression.

Table 2
Univariate and multivariate analysis for OS and CSS in all patients who underwent nephrectomy ($n = 699$)

Characteristics	OS				CSS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years) (<65/>65)	1.64 (1.20−2.24)	0.002*	−	ns	1.29 (0.89−1.85)	0.17		
BMI (<22.4/>22.4)	1.58 (1.16−2.13)	0.003*	−	ns	1.67 (1.17−2.38)	0.005*	−	ns
Sex (male/female)	1.36 (0.98−1.86)	0.07			1.56 (1.08−2.24)	0.012*	−	ns
ECOG-PS (0/>1)	5.84 (4.20−8.04)	<0.001*	2.04 (1.38−3.01)	<0.001*	7.97 (5.50−11.46)	<0.001*	2.03 (1.31−3.14)	0.002*
T classification (1-2/3-4)	5.75 (4.23−7.79)	<0.001*	1.87 (1.27−2.77)	0.002*	8.94 (6.25−12.89)	<0.001*	1.96 (1.84−3.00)	0.002*
N classification (0/1)	5.97 (3.92−8.79)	<0.001*	−	ns	7.76 (4.96−11.73)	<0.001*	−	ns
Histology type (clear/others)	1.53 (0.95−2.35)	0.08			1.60 (0.93−2.61)	0.09		
Tumor size (cm) (<4.0/>4.0)	3.49 (2.46−5.08)	<0.001*		ns	11.51 (6.35−23.48)	<0.001*	2.50 (1.21−5.18)	0.014*
Nuclear grade (1-2/3-4)	4.25 (3.13−5.77)	<0.001*	−	ns	6.86 (4.27−11.05)	<0.001*	-	ns
Metastasis at diagnosis (-/+)	12.84 (9.09−17.97)	<0.001*	3.63 (2.37−5.55)	<0.001*	20.64 (14.05−30.25)	<0.001*	4.55 (2.85−7.29)	<0.001*
UISS (Low/intermediate-high)	6.15 (4.33−8.91)	<0.001*	1.67 (1.02−2.76)	0.042*	15.55 (9.09−29.03)	<0.001*	2.65 (1.31−5.34)	0.007*
NLR (<3.38/>3.38)	2.74 (2.00−3.73)	<0.001*	−	ns	3.42 (2.38−4.88)	<0.001*	−	ns
PLR (<192/>192)	2.43 (1.79−3.30)	<0.001*	−	ns	2.98 (2.09−4.25)	<0.001*	−	ns
CAR (<0.073/>0.073)	4.29 (3.15−5.92)	<0.001*	2.33 (1.65−3.33)	<0.001*	5.80 (3.97−8.65)	<0.001*	2.51 (1.64−3.84)	<0.001*

BMI, body mass index; CAR, C-reactive protein to albumin ratio; CI, confidence interval; CSS, cancer-specific survival; ECOG-PS, eastern cooperative oncology group-performance status; HR, hazard ratio; NLR, neutrophil count to lymphocyte count ratio; ns, nonsignificant; OS, overall survival; PLR, platelet lymphocyte ratio; UISS, UCLA integrated staging system; *$P < 0.05$.

4. Discussion

In the present study, we assessed the prognostic value of preoperative CAR in patients with RCC, who underwent nephrectomy. The results consistently showed that the increasing CAR was significantly associated with shorter OS, CSS and RFS, and serves as an independent prognostic factor for patients with RCC after surgery. Recently, several studies have shown a relationship between CAR and prognosis in patients with various types of cancers including RCC [25−28]. Chen et al. reported the prognostic value of CAR on overall survival (OS) of patients with clear cell renal carcinoma [20]. Guo et al., subsequently, reported that an elevated CAR was an independent prognostic factor for poor OS in RCC patients who underwent radical or partial nephrectomy and disease-free survival of localized RCC patients who underwent nephrectomy [21]. The current study was intended to assess the prognostic value of preoperative CAR in Japanese patients with RCC by multi-institutional cohort datasets in which 699 patients

Table 3
Univariate and multivariate analysis for RFS in patients who had no metastasis at the time of nephrectomy ($n = 627$)

Characteristics	RFS			
	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years) (≤65/>65)	1.38 (0.97−1.95)	0.073		
BMI (≤22.4/>22.4)	1.75 (1.24−2.46)	0.001	1.53 (1.08−2.17)	0.017*
Sex (male/female)	1.36 (0.94−1.93)	0.102		
ECOG-PS (0/≥1)	2.20 (1.31−3.49)	0.004*	−	ns
T classification (1-2/3-4)	4.80 (3.33−6.85)	<0.001*	2.54 (1.60−4.07)	<0.001*
N classification (0/1)	5.73 (2.90−10.16)	<0.001*	−	ns
Histology type (clear/others)	1.03 (0.55−1.75)	0.922		
Tumor size (cm) (≤4.0/>4.0)	3.83 (2.60−5.79)	<0.001*	2.29 (1.47−3.64)	<0.001*
Nuclear grade (1-2/3-4)	3.49 (2.43−4.95)	<0.001*	1.77 (1.12−2.81)	0.015*
UISS (Low/intermediate-high)	3.48 (2.47−4.94)	<0.001*	−	ns
NLR (≤3.38/>3.38)	2.35 (1.62−3.37)	<0.001*	1.68 (1.11−2.51)	0.012*
PLR (≤192/>192)	2.23 (1.57−3.15)	<0.001*	−	ns
CAR (≤0.073/>0.073)	2.58 (1.84−3.61)	<0.001*	1.51 (1.04−2.19)	0.029*

BMI, body mass index; CAR, C-reactive protein to albumin ratio; CI, confidence interval; ECOG-PS, eastern cooperative oncology group-performance status; HR, hazard ratio; NLR, neutrophil count to lymphocyte count ratio; ns, nonsignificant; PLR, platelet lymphocyte ratio; RFS, recurrence-free survival; UISS, UCLA integrated staging system; *$P < 0.05$.

Table 4
Comparison of the AUCs between prognostic models

	CSS (all)		RFS (localized)	
	AUC (95%CI)	*P* value	AUC (95%CI)	*P* value
CAR	0.82 (0.75−0.87)	Ref	0.69 (0.62−0.75)	Ref
NLR	0.73 (0.67−0.78)	0.027*	0.66 (0.59−0.71)	ns
PLR	0.72 (0.66−0.78)	0.013*	0.65 (0.58−0.71)	ns
GPS	0.78 (0.73−0.83)	ns	0.64 (0.59−0.69)	0.029*
mGPS	0.78 (0.73−0.83)	ns	0.64 (0.59−0.69)	0.031*
UISS	0.87 (0.83−0.90)	ns	0.70 (0.64−0.75)	ns

AUC, area under the curve; CAR, C-reactive protein to albumin ratio; CI, confidence interval; CSS, cancer-specific survival; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil count to lymphocyte count ratio; ns, nonsignificant; PLR, platelet lymphocyte ratio; RFS, Recuurence-free survival; UISS, UCLA integrated staging system; *$P < 0.05$.

were assigned, and the results further supported the previous studies, indicating the utility of CAR as a prognostic factor. The present study also showed that the CAR was a valuable predictor for the relapse compared to the other inflammatory based scoring models. Furthermore, our findings suggested that the CAR might be a prognostic factor in M1 RCC patients who underwent nephrectomy, which is consistent with the studies by Chen et al. and Guo et al. [20,21].

Recent studies demonstrated systemic inflammatory status has a correlation with reactive thrombocytosis in several types of cancer including RCC [29,30]. Thrombocytosis is induced in 10−57% of patients with cancer [31]. Interleukin-6 (IL-6) has been reported to play an important role in reactive thrombocytosis, stimulating elevated CRP level in the liver [32]. In addition, the thrombocytosis is also induced by the tumor itself. Several studies have revealed that vascular endothelial growth factor stimulates megakaryocyte differentiation [33]. It is plausible that VEGF plays a critical role in tumor growth for RCC, quantitative evaluation of thrombocytosis might reflects tumor progression serving as a surrogate marker of tumor burden [34]. As shown in Table 4, we compared AUCs for predicting CSS and RFS in those systemic inflammatory biomarkers including NLR, PLR, GPS, mGPS and CAR. The results demonstrated that CAR seems to be a reliable predictor of CSS compared with NLR and PLR, as well as RFS compared with GPS and mGPS.

In the present study, we applied UISS, well-known prognostic scoring model [24], to compare the predictive value of CAR on multivariate analysis. In addition, AUC analysis demonstrated that CAR was comparable to UISS. The UISS score was proposed from UCLA, and the score is assigned by tumor stage, Fuhrman grade and ECOG-PS. The scoring model includes perioperative and pathological findings such as Fuhrman grade and ECOG-PS. The CAR, on the other hand, simply consists of serum CRP level and Alb level, both of which are routinely collected in preoperative blood draw. Therefore, CAR might render an objective premise prior to the treatment in patients with operable RCC, which potentially allows physicians to consider other possible treatment options such as targeted neoadjuvant or adjuvant therapy in patients with higher CAR. Nevertheless, recent reports indicated that adjuvant molecular targeted therapy of sunitinib was still controversial [2]. In addition, neoadjuvant therapy using approved molecular targeted agents such as pazopanib [35,36], axitinib [37], sunitinib [38], and sorafenib [39] also could not offer survival benefit in RCC. Preoperative assessment using CAR might offer valid information for identifying patients who are more likely to benefit from those therapies prior to surgery.

The limitations in the present study include its retrospective design and missing information of use of molecular targeted therapies which could affect the prognosis in RCC. Multi-institutional and prospective randomized controlled trials are warranted to confirm our preliminary findings.

5. Conclusion

In summary, we showed that an elevated CAR was associated with shorter patient survivals and an independent predictor for OS, CSS and RFS in RCC patients with and without metastasis at the time of nephrectomy. Since the CAR can be measured preoperatively, this system should be incorporated in routine diagnosis for risk stratification and treatment decision-making of operable RCC patients.

Conflicts of interest

The authors declare no conflicts of interest.

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