C-reactive Protein-albumin-lymphocyte Index as a Novel Biomarker for Progression in Patients Undergoing Surgery for Renal Cancer

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Abstract. *Background/Aim: Some patients with renal cell carcinoma (RCC) develop early or late recurrence after surgery. However, there is no clear consensus on which patients with postoperative RCC should be treated. This study aimed to establish a biomarker for selecting patients who are at a higher risk of relapse following renal cancer surgery. Patients and Methods: A total of 378 patients who underwent nephrectomy or partial nephrectomy for a diagnosis of RCC at our hospital were included, with a focus on pT3 cases at high risk of recurrence. Factors associated with postoperative progression, including pathological and hematological parameters, were examined. Results: Sarcomatoid features, Fuhrman grade 4, and C-reactive protein-albumin-lymphocyte (CALLY) index were statistically significant predictive factors for progression-free survival after surgery (p<0.0011, p=0.0047, and p<0.0001, respectively). In the multivariate Cox proportional regression analysis, the CALLY index was the most statistically significant predictor of the risk of postoperative recurrence (p=0.0002). Conclusion: In addition to the existing risk factors for RCC recurrence, such as sarcomatoid features and Fuhrman grade, we propose that the CALLY index is a predictor of postoperative recurrence and that patients with a low CALLY index are good candidates for postoperative treatment. Our study may help select patients with pT3 disease with a high risk of recurrence who require postoperative treatment.*

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Renal cell carcinoma (RCC) accounts for 2% of all cancer cases and deaths worldwide (1). Approximately 75% of RCC cases are clear cell RCC (ccRCC), which is the leading cause of cancer-specific mortality (2, 3). Localized RCC can be treated using partial or radical nephrectomy. Treatment of metastatic RCC may be preceded by immediate nephrectomy for tumor shrinkage or delayed nephrectomy after medical therapy; however, the timing of nephrectomy remains controversial. Certain clinical parameters are associated with an increased risk of recurrence. For example, the primary tumor stage is a known prognostic factor. Up to 26% of patients with stage T2 disease, approximately 50% of patients with stage T3 disease, and almost all patients with stage T4 disease relapse after nephrectomy (4, 5). Higher nuclear grades and sarcomatoid features have also been independently associated with an increased risk of RCC recurrence (6). C-reactive protein (CRP) levels and the neutrophil-to-lymphocyte ratio (NLR) are prognostic factors that have been reported to be associated with renal cancer recurrence (7, 8). Recently, the CRP-albumin-lymphocyte (CALLY) index, calculated from the results of CRP, albumin, and lymphocyte blood sampling, has been shown to be a useful prognostic marker in gastrointestinal cancers and a predictor of cancer recurrence (9, 10); however, its use for renal cancer has not been reported. Therefore, for the first time, we examined whether the CALLY index can predict postoperative recurrence in patients with renal cancer.

In this study, we investigated whether the CALLY index, which has been reported as a prognostic marker in other cancers, could be a predictor of postoperative RCC recurrence in patients with pT3 tumors with a high RCC recurrence rate. If the CALLY index is a better predictive marker of recurrence than current pathological factors, it can

Table I. *Patient characteristics (n=378).*

Variable		
Sex	n (%)	
Male	255 (67.5)	
Female	123 (32.5)	
Age (years)		
Median	66	
Range	28-92	
TNM stage	n (%)	
T1	279 (73.8)	
T2	18 (4.8)	
T3	80 (21.2)	
T4	1 (0.2)	
N0	370 (97.9)	
N1	6 (1.6)	
N2	2 (0.5)	
M0	361 (95.5)	
M1	17 (4.5)	
Fuhrman grade		
G1	128 (33.9)	
G2	192 (50.8)	
G3	44 (11.6)	
G4	14 (3.7)	
Follow-up	Duration (month)	
Median	93.5	
Range	1-542	
Outcome		
Progression	n (%)	
No	317 (83.9)	
Yes	61 (16.1)	
Overall survival	n (%)	
Survival	334 (91.0)	
Death	44 (9.0)	

Table II. *Patient characteristics (T3, n=80).*

Variable		
Sex	n	%
Male	55	68.75
Female	25	31.25
Age (years)		
Median	65.5	
Range	40-90	
TNM stage		
T3a	72	90
T3b	7	8.75
T3c	1	1.25
N0	73	91.25
N1	5	6.25
N2	2	2.5
M0	67	83.75
M1	13	16.25
Fuhrman grade		
G1	16	20
G2	32	40
G3	22	27.5
G4	10	12.5
Sarcomatoid feature		%
No	70	87.5
Yes	10	12.5
Tumor specific necrosis		
No	49	61.25
Yes	31	38.75
Post-op lab data	n	%
NLR		
>3	28	35
≤3	52	65
CRP		
>3	22	27.5
≤3	58	72.5
CALLY index		
>1.28	40	50
≤1.28	40	50
Outcome	n	%
Progression		
No	49	61.25
Yes	31	38.75
Overall survival		
Survival	65	81.25
Death	15	18.75

NLR: Neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; CALLY: C-reactive protein-albumin-lymphocyte.

be used to narrow down cases that are a valid choice for adjuvant treatment of renal cancer.

Patients and Methods

Patients and Methods. This study included 378 patients who underwent partial or radial nephrectomy at the Yamaguchi University Hospital between October 2005 and September 2023. All patients were pathologically diagnosed with ccRCC. The detailed patient characteristics are shown in Table I. This study was approved by the Institutional Ethics Committee of the Graduate School of Medicine, Yamaguchi University (IRB #2023-042). Written informed consent was obtained from all participants enrolled in the study.

Clinical and laboratory assessments. Clinical and pathological data, including age, sex, serum albumin, serum C-reactive protein levels, neutrophil counts, pathological factors (sarcomatoid features, tumor-specific necrosis, and Fuhrman grade), and survival data [progression-free survival (PFS) and overall survival (OS)], were evaluated.

The CALLY index was defined as the serum albumin level (g/dl)×absolute lymphocyte count (cells/μl)/CRP level (mg/dl). In particular, for pT3 cases (n=80; Table II), we examined when postoperative recurrence occurred, assessed which clinical factors were most associated with postoperative recurrence, and identified the risk factors associated with progression using multivariate analysis.

Statistical analysis. PFS and OS rates were calculated using the Kaplan-Meier method, and differences between the two groups were analyzed using the log-rank test. Multivariate analyses were performed to assess predictors of PFS and OS based on clinical and pathological factors using the Cox proportional hazards method. All statistical analyses were performed using the JMP Pro 16 software (version 16.0; SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at *p*<0.05.
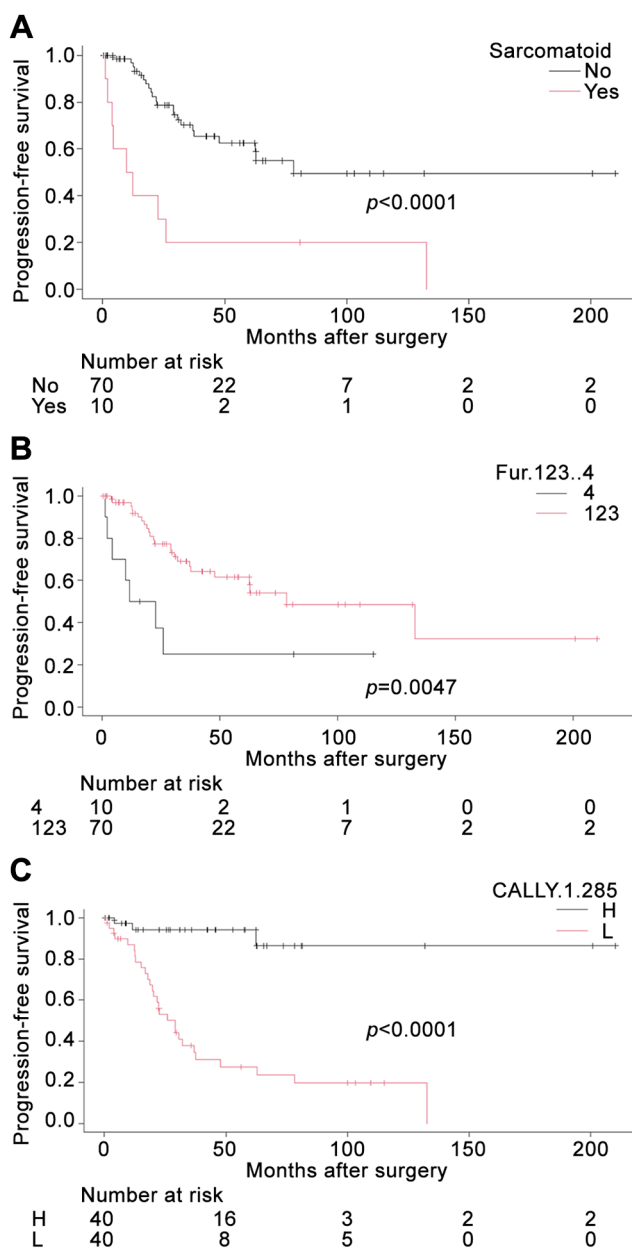
Figure 1. *Kaplan-Meier curves of progression-free survival (PFS) in patients with pT3 clear cell renal cell carcinoma (n=80). (A) Sarcomatoid feature. (B) Fuhrman grade 1, 2, and 3 vs. 4. (C) CALLY index (median 1.285).*

Results

Study population. This study included 378 patients who had undergone nephrectomy or partial nephrectomy owing to the diagnosis of ccRCC at the hospital. Of the 378 patients with RCC, 80 (21.2%) had pT3, eight (2.1%) had lymph node metastases, and 17 (4.5%) had organ metastases. The median overall follow-up period was 93.5 months, with a maximum of 542 months; 61 (16.1%) patients had postoperative recurrence, and 334 (88.35%) were overall survivors (Table I).

PFS and OS. In this study, we investigated the correlation between various factors, including the CALLY index and PFS and OS in pT3 cases, to explore the multiple factors involved in postoperative recurrence and to determine which patients should be actively treated with adjuvant therapy. Table II shows the details of the pT3 cases; 31 (39%) of the 80 cases had postoperative recurrence, sarcomatoid features were present in 10 (12.5%), and Fuhrman grade 4 in 10 (12.5%). Fuhrman grade 4, sarcomatoid features, and postoperative CALLY index <1.285 were identified as predictive factors using the Kaplan-Meier log-rank test for PFS (Figure 1).

Cox proportional hazards analysis. In the multivariate Cox proportional hazards analysis, both sarcomatoid features and the CALLY index remained statistically significantly prognostic. Although not statistically significant, the Fuhrman grade 4 suggested an association (Table III). The univariate analysis showed that four factors (metastases, Fuhrman grade 4, sarcomatoid features, and the CALLY index) were significantly predictive of OS ($p=0.0454$, $p=0.0242$, $p=0.0446$, and $p=0.0276$, respectively). However, these four factors showed no statistical significance in the multivariate analysis (Table IV).

Association of CALLY index with several parameters. In the present study, the CALLY index was the most important marker of postoperative recurrence; therefore, the relationship between the existing recurrence markers and the CALLY index was investigated (Table V). Among T3 cases, the CALLY index was significantly lower in T3b/T3c cases than in T3a cases, and the CALLY index was also significantly lower in cases with sarcomatoid features than in cases without sarcomatoid features ($p=0.007$ and $p=0.0232$, respectively).

Discussion

This study investigated the patient population requiring postoperative adjuvant treatment among patients with ccRCC using various factors. As reported previously, the risk of recurrence is high in patients with large T stage, lymph node metastases, distant metastases, and pathological sarcomatoid features after surgery (4-6). As inflammatory responses play a central role in RCC tumor growth and metastasis, several laboratory parameters, including CRP, NLR, and platelet-lymphocyte ratio, have been reported as useful prognostic markers (7, 8, 11). These factors have also been examined as therapeutic predictive markers for the efficacy of immune checkpoint inhibitors. There have been reports of an association between pretreatment CRP and NLR and the efficacy of immune checkpoint inhibitor treatment; however,

Table III. *Univariate and multivariate analysis to predict progression-free survival in pT3 patients.*

Category		Univariate analysis		Multivariate analysis	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Characteristics					
Sex	Male *vs.* female	0.8264463 (0.3959969-1.7247945)	0.6116		
Age (median 65 yr)	Older *vs.* younger	1.3846154 (0.678441-2.8258311)	0.3713		
BMI (median 23.1)	High *vs.* low	1.0666667 (0.5273621-2.1574888)	0.8575		
Stage					
pT3	T3bc *vs.* T3a	1.7307692 (0.6646239-4.5071536)	0.2613		
N	N1+2 *vs.* N0	1.8271605 (0.6393495-5.2217377)	0.2606		
M	M1 *vs.* M0	1.2369231 (0.507436-3.0151163)	0.64		
Pathology					
Fuhrman grade	4 *vs.* 1+2+3	2.0416667 (0.8797124-4.73837)	0.0966		
Sarcomatoid feature	Yes *vs.* no	2.8636364 (1.3185944-6.2190675)	0.0078	2.7978743 (1.2262304-6.3838742)	0.0145
Tumor specific necrosis	Yes *vs.* no	1.3017078 (0.6416689-2.6406815)	0.465		
Post-op data					
CALLY index (median 1.28) (1 week after operation)	Low *vs.* high	9.2171156 (3.2110994-26.45674)	<0.0001	7.7130305 (2.6442986-22.497777)	0.0002

HR: Hazard ratio; BMI: body mass index; CALLY: C-reactive protein-albumin-lymphocyte.

Table IV. *Univariate and multivariate analysis to predict overall survival in pT3 patients.*

Category		Univariate analysis		Multivariate analysis	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Characteristics					
Sex	Male *vs.* female	1.0003628 (0.3338219-2.9977832)	0.9995		
Age (median 65 yr)	Older *vs.* younger	1.802436 (0.643428-5.0491673)	0.2623		
BMI (median 23.1)	Low *vs.* high	1.3250422 (0.4706965-3.7300824)	0.5941		
Stage					
pT3	T3bc *vs.* T3a	1.8082779 (0.5067913-6.4521016)	0.3614		
N	N1+2 *vs.* N0	3.6156991 (0.791479-16.517533)	0.0973		
M	M1 *vs.* M0	3.0764487 (1.0231252-9.2506138)	0.0454	2.3125047 (0.6805486-8.2769766)	0.1751
Pathology					
Fuhrman grade	4 *vs.* 1+2+3	3.8454976 (1.192015-12.40576)	0.0242	1.8675486 (0.467112-7.466592)	0.4657
Sarcomatoid feature	Yes *vs.* no	3.281913 (1.0290843-10.466541)	0.0446	2.1344058 (0.5075035-8.9766634)	0.3099
Tumor-specific necrosis	Yes *vs.* no	0.6620087 (0.2095931-2.0909831)	0.4821		
Post-op data					
CALLY index (median 1.28) (1 week after operation)	Low *vs.* high	4.2686376 (1.1740373-15.520178)	0.0276	3.0326176 (0.7911034-11.625243)	0.1056

HR: Hazard ratio; BMI: body mass index; CALLY: C-reactive protein-albumin-lymphocyte.

the results for each factor have been conflicting in some reports, and precise prognostic markers remain unclear. Therefore, we first investigated preoperative and postoperative CRP and NLR in relation to postoperative recurrence but found no markers that were better predictors of recurrence than pathological parameters such as sarcomatoid features or Fuhrman grade (data not shown). Subsequently, we focused on the CALLY index as a predictor of recurrence, which includes several factors (9, 10). We investigated its usefulness as a predictive marker for the postoperative recurrence of RCC. The CALLY index was first reported in liver cancer (12) as a new prognostic factor that combines factors such as immunity, nutrition, and inflammation. Its usefulness as a prognostic marker has since been reported in gastric (13) and esophageal (9, 10) cancers. However, to date, no study has reported the prognostic value of the CALLY index in patients with renal cancer, and this is the first study to do so.

Table V. *Association of CALLY Index with several clinical factors.*

	n	CALLY index (mean)	Wilcoxon/ Kruskal-Wallis test *p*-Value
TNM stage			
T3a	72	4.852	Reference
T3b	7	1.185	0.007
T3c	1	0.3693	
N0	73	4.767	Reference
N1 N2	7	0.878	0.0512
M0	67	4.899	Reference
M1	13	2.288	0.2733
Fuhrman grade			
G1/G2/G3	70	4.335	Reference
G4	10	5.452	N.S.
Sarcomatoid feature			
No	70	4.979	Reference
Yes	10	0.945	0.0232
Tumor-specific necrosis			
No	49	5.085	Reference
Yes	31	3.511	N.S.

CALLY: C-reactive protein-albumin-lymphocyte.

Our findings may be clinically useful. Postoperative adjuvant treatment for patients with RCC was first investigated with molecularly targeted agents, followed by clinical trials with immune checkpoint inhibitors; pembrolizumab is only allowed in patients at high risk of recurrence after surgery (14). The Keynote 564 trial showed significantly increased disease-free survival in patients at high risk of postoperative recurrence with pembrolizumab as adjuvant therapy than in those without (median disease-free survival not reached in the pembrolizumab group; hazard ratio=70.68; 95% confidence interval=0.53-0.87; *p*=0.0010), making the use of pembrolizumab in patients at high risk of recurrence (pT3, pT4, N0M0; lymph node metastasis; pT2 grade 4 or sarcomatoid features+N0M0, M1NED) acceptable (14). This study investigated the association between these risk factors and the CALLY index. The CALLY index was significantly low in T3b and T3c cases. The CALLY index was also low in N1 and M1 cases, although not significantly, and it was significantly low in cases with sarcomatoid features, suggesting that the CALLY index may be useful as a predictive marker for recurrence. The CALLY index may be closely related to factors associated with postoperative recurrence.

Study limitations. First, the number of patients was small, and the data were analyzed retrospectively. Second, the study included cases from 2005 to 2023; therefore, preoperative treatment methods were not standardized owing to changes in treatment strategies over this period. The third limitation was the method used to determine the CALLY index. In the present study, the classification was based on intermediate values; however, further consideration is needed to determine where the cutoff value should be set as the number of cases increases. Although the potential of the CALLY index as a prognostic marker has been demonstrated, whether immune checkpoint inhibitors can prevent postoperative recurrence in patients with a low CALLY index remains unclear.

Conclusion

We focused on patients with pT3 tumors at high risk of postoperative recurrence and showed that the CALLY index is a significantly better predictor of recurrence than the existing pathological risk factors for cancer recurrence after surgery. Further case series are needed, but we believe that our results can help select patients at high risk of postoperative recurrence and identify targets for treatment.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contributions

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