ORIGINAL

Value of the CRP–albumin ratio in patients with resectable pancreatic cancer

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Abstract : Background : The C-reactive protein (CRP)–albumin ratio (CAR) was reported as a prognostic factor of resectable hepatocellular carcinoma. The aim of this study was to analyse the significance of CAR in resectable pancreatic cancer. Patients and Methods : 163 patients with curative resection for pancreatic cancer were enrolled in this retrospective study. Cases of non-curative resection were excluded. The CAR was calculated with the preoperative plasma CRP and albumin values, with a cut-off value of 0.06, as calculated in a previous report. Results : Patients in the low CAR group had significantly better overall survival (OS) and disease-free survival (DFS) compared with the high CAR group ($P<0.05$). On multivariate analysis, for high CAR, CA19-9 >300 U/ml and receipt of adjuvant chemotherapy were independent risk factors for OS and DFS. High CAR was significantly associated with advanced T stage. Conclusion : The CAR might be a prognostic factor for patients with resectable pancreatic cancer. J. Med. Invest. 68 : 244-248, August, 2021

Keywords **:** *Pancreas cancer, C-reactive protein, albumin*

INTRODUCTION

The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) is extremely poor. Despite the development of surgical techniques and perioperative chemotherapy, the 5-year survival rate is 8% in the United States (1). PDAC is also the fifth most common cause of cancer death in Japan (2). The frequency of postoperative recurrence remains high in patients with PDAC (3) ; therefore, a novel prognostic marker to predict recurrence is required.

Nowadays, tumour-related pathological factors have been identified as predictive markers in patients with PDAC, including tumour stage, lymph node metastasis, vascular and lymphatic invasion and perineural invasion. Several predictive markers based on preoperative systemic inflammation and nutritional status such as the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), modified Glasgow prognostic score (mGPS), and prognostic index (PNI) were reported in lung cancer (4), hepatocellular carcinoma (5), melanoma (6), renal cell carcinoma (7), gastric cancer (8), intrahepatic cholangiocarcinoma (9) and colorectal cancer (10). These factors has been reported as useful biomarker to predict the prognosis in PDAC (11, 12).

C-reactive protein (CRP) to albumin ratio is based on two acute inflammatory protein (13). The CRP–albumin ratio (CAR) was reported as a prognostic factor of resectable hepatocellular carcinoma, colorectal cancer, oesophageal cancer, gastric cancer, renal cancer, and pancreatic cancer (14-18).

The aim of this study was to analyse and validate the significance of the CAR in resectable pancreatic cancer at our hospital.

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PATIENTS AND METHODS

One hundred sixty-three patients who underwent curative surgical resection for PDAC during 2004 to 2018 at the University of Tokushima Hospital were enrolled in this retrospective study. Fourteen patients were excluded because of non-curative resection. All the patients had PDAC proven histologically. Finally, 149 patients were analysed in this study. Laboratory data including serum CRP and albumin were collected within 1 month before surgery. Patients were followed up monthly for tumour markers including CEA and CA19-9 and underwent computed tomography every 4–6 months. When recurrence was suspected, precise diagnostic imaging studies including positron emission tomography were performed. After confirmation of recurrent pancreatic cancer, systemic chemotherapy, radiation therapy, or best supportive care were indicated. The clinicopathological characteristics of the patients are shown in Table 1. All patients signed informed consent for this study, which was approved by the clinical ethics committee at our institution (#3362).

The NLR, PNI, PLR, and mGPS were calculated with cutoff values of 3, 45, 150, and 1, respectively. The CAR was also calculated. To determine the appropriate cutoff value of CAR, receiver operation characteristic (ROC) curve analysis was performed. The cutoff value of CAR was 0.06 and the AUC value was 0.54223.

Statistical analysis

Statistical comparisons for significance were made using chi-squared test or Fisher's exact test with one degree of freedom, as appropriate. Cumulative patient survival and recurrence-free survival were determined using the Kaplan–Meier method with a log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazard model. A *P*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with JMP 14 software (SAS Institute, Cary, NC, USA).

Table 1. Clinicopathological characteristics of patients with surgical resection for pancreas ductal adenocarcinoma

Parameters	
Age, years	70 (63-76)
female / male	77 (51.7) / 72 (48.3)
Body mass index kg/m^2	22.1 (19.7-24.2)
Fibrinogen, g/ml	439 (367-510)
C reactive protein, mg/L	0.09 (0.05-0.27)
Serum albumin, g/dl	3.9 (3.7-4.2)
WBC, 10^9/L	5450 (4400-6600)
Neutrophils, 10^9/L	3650 (2600-4495)
Lymphocytes, 10^9/L	1290 (1040-1715)
CEA ng/ml	2.3 (1.4-3.9)
CA19-9 U/ml	126 (27.5-670)
Type of resection (DP/PD/TP)	40/56/4
PV resection (n, %)	22 (14.7)
Neoadjuvant chemotherapy (n, %)	16 (10.7)
Postoperative chemotherapy (n, %)	89 (59.3)
UICC stage (n, %)	
ⅠA	20 (15.4)
ⅠB	16 (16)
ⅡA	47 (31.5)
ⅡB	43 (28.9)
Ⅲ	23 (15.4)
Resection margin R0	115 (76.7)
Tumor size ≥ 2cm	113 (75.6)
Lymph node metastasis (n)	52 (35.1)
Lymphatic invasion (ly)	100 (68.0)
Vascular invasion (v)	114 (77.6)
Perineural invasion (ne)	119 (81.5)
Anterior serosal invasion (s)	34 (29.6)
Retroperitoneal invasion (rp)	45 (38.1)
Microscopic portal vein invasion (pv)	23 (22.3)
Microscopic arterial invasion (a)	6 (5.7)
Plexus invasion (pl)	11 (12.5)

Data are expressed as median (IQR) or n(%)

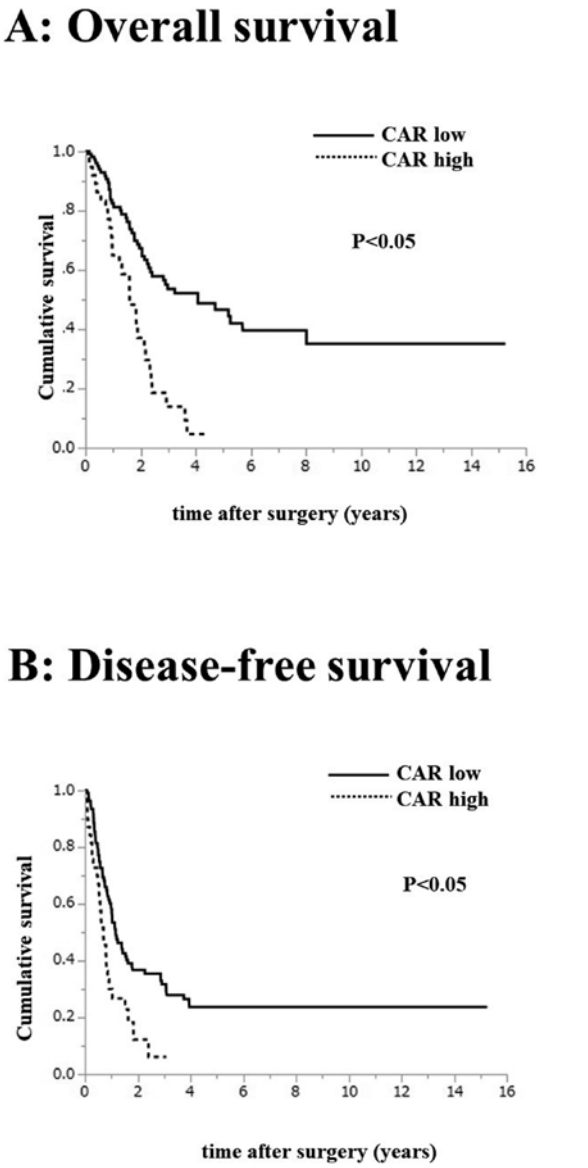

Figure 1. Kaplan–Meier curves of overall survival and disease-free survival according to CAR. (A) Overall survival. (B) Disease-free survival.

RESULTS

Comparison of prognostic factors for overall survival (OS) in patients with surgical resection for PDAC

The OS rate was significantly worse in patients with a high CAR compared with those with a low CAR (Figure 1A). The prognostic factors for OS in patients with surgical resection for PDAC is shown in Table 2. In the univariate analysis, seven factors were independent prognostic factors for OS including CAR (HR 2.826, 95% CI 1.720–4.645, $P < 0.001$), PNI (HR 2.250, 95% CI 1.384–3.645, $P = 0.0007$), PLR (HR 1.643, 95% CI 1.022–2.684, $P = 0.0045$), CA19-9 (HR 2.085, 95% CI 1.314–3.311, $P = 0.0013$), adjuvant chemotherapy (HR 2.208, 95% CI 1.396–3.491, $P = 0.0022$), T3+4 (HR 2.873, 95% CI 1.700–5.114, $P < 0.001$), and lymph node metastasis (HR 1.846, 95% CI 1.143–2.945, P = 0.0095). In the multivariate analysis of these seven factors, three factors were independent prognostic factors for OS including CAR (HR 2.668, 95% CI 1.523–4.672), CA19-9 (HR 2.011, 95% CI 1.213–3.334), and adjuvant chemotherapy (HR 2.231, CI 1.379–3.609).

Comparison of prognostic factors for disease-free survival (DFS) in patients with surgical resection for PDAC

The DFS rate was significantly worse in patients with a high CAR compared with those with a low CAR (Figure 1B). The prognostic factors for DFS with surgical resection for PDAC are shown in Table 3. In the univariate analysis, five factors were independent prognostic factors for DFS including CAR (HR 2.826, 95% CI 1.720–4.645, $P < 0.001$), PNI (HR 1.542, 95% CI 1.008–2.340, $P = 0.0308$), CA19-9 (HR 1.864, 95% CI 1.239–2.797, $P = 0.0031$), adjuvant chemotherapy (HR 1.884, 95% CI 1.257–2.824, $P = 0.0020$), and T(3+4) (HR 1.890, 95% CI 1.232–2.966, $P = 0.0032$). In the multivariate analysis of these five factors, three factors were independent prognostic factors for DFS including CAR (HR 1.990, 95% CI 1.198–3.307, $P = 0.0103$), CA19-9 (HR 1.864, 95% CI 1.239–2.797, $P = 0.0083$), and adjuvant chemotherapy (HR 1.884, 95% CI 1.257–2.824, $P = 0.0032$).

Clinicopathological features according to the CAR

Clinicopathological factors were compared between the high CAR and low CAR groups in Table 4. The high CAR group was correlated with higher CRP, lower serum albumin, higher serum fibrinogen, low LCR, high NLR, low PNI and high mGPS. In the tumour-related factors, the high CAR group was significantly associated with T (3+4). Also, the high CAR group showed an association with portal vein resection and adjuvant chemotherapy but this was not significant. The other factors showed no significant difference between these two groups.

Table 2. OS related variables

		Univariate		Multivariate	
Factor		p-value	HR (95% CI)	p-value	HR (95% CI)
CAR	< 0.06/ ≥ 0.06	< 0.001	2.826 (1.720-4.645)	0.0006	2.668 (1.523-4.672)
LCR	< 15090/ ≥ 15090	0.0505	1.593 (0.390-1.007)		
NLR	< 3/ ≥3	0.941	1.021 (0.603-1.672)		
PNI	< 45/ ≥ 45	0.0007	2.250 (1.384-3.645)	0.3571	1.282 (0.755-2.175)
PLR	< 150/ ≥ 150	0.0045	1.643 (1.022-2.684)	0.6254	1.139 (0.675-1.923)
mGPS	0 / 1,2	0.6799	2.270 (0.806-5.190)		
Gender	Female/male	0.7023	1.315 (0.829-2.087)		
Age	< 70/ ≥ 70	0.1558	1.391 (0.874-2.201)		
BMI kg/m^2	< 25/ ≥ 25	0.5203	1.216 (0.639-2.143)		
CEA ng/ml	< 5/ ≥ 5	0.5878	1.203 (0.578-2.248)		
CA19-9 U/ml	< 300/ ≥ 300	0.0013	2.085 (1.314-3.311)	0.0068	2.011 (1.213-3.334)
Resection type	PD/DP/TP	0.4474	1.190 (0.726-1.951)		
PV resection	No/yes	0.4731	1.310 (0.575-2.600)		
NAC(-)	No/yes	0.9223	1.039 (0.433-2.116)		
AC(-)	No/yes	0.0022	2.208 (1.396-3.491)	0.0011	2.231 (1.379-3.609)
T(3+4)	No/yes	< 0.001	2.873 (1.700-5.114)	0.0870	1.539 (0.906-3.166)
N(+)	No/yes	0.0095	1.846 (1.143-2.945)	0.0987	1.693 (0.906-3.166)

Table 3. DFS related variables

		Univariate		Multivariate	
Factor		p-value	HR (95% CI)	p-value	HR (95% CI)
CAR	<0.06/ ≥ 0.06	< 0.001	2.826 (1.720-4.645)	0.0103	1.990 (1.198-3.307)
LCR	<15090/ ≥ 15090	0.0030	1.843 (0.357-0.822)		
NLR	< 3/ ≥ 3	0.3812	1.176 (0.759-1.792)		
PNI	< 45/ ≥ 45	0.0308	1.542 (1.008-2.340)	0.6387	1.113 (0.708-1.735)
PLR	< 150/ ≥ 150	0.2235	1.270 (0.840-1.928)		
mGPS (0/1+2)	0 / 1,2	0.0529	1.956 (0.662-4.642)		
Gender (F/M)	Female / male	0.9196	1.040 (0.698-1.553)		
Age > 70	< 70/ ≥ 70	0.4904	1.176 (0.780-1.759)		
BMI > 25 kg/m^2	< 25/ ≥ 25	0.3700	1.295 (0.729-2.158)		
CEA > 5 ng/ml	< 5/ ≥ 5	0.1032	1.604 (0.886-2.713)		
CA19-9 > 300 U/ml	< 300/ ≥ 300	0.0031	1.864 (1.239-2.797)	0.0083	1.802 (1.166-2.776)
PD/DP/TP	PD/DP/TP	0.4415	1.322 (0.850-2.058)		
PV resection	No/yes	0.1937	1.466 (0.809-2.478)		
NAC(-)	No/yes	0.4135	1.306 (0.709-2.405)		
AC(-)	No/yes	0.0020	1.884 (1.257-2.824)	0.0032	1.884 (1.245-2.851)
T(3+4)	No/yes	0.0032	1.890 (1.232-2.966)	0.0646	1.548 (0.974-2.514)
N(+)	No/yes	0.0561	1.494 (0.979-2.252)		

Table 4. CAR related variables

Factor	CAR High (n=38)	CAR Low (n=111)	p-value
Age ≥ 70	18 (47.7)	53 (47.6)	0.9678
Male gender	21 (55.3)	51 (45.6)	0.3211
BMI ≥ 25 kg/m^2	7 (18.4)	15 (13.5)	0.4706
CEA ≥ 5 ng/ml	8 (21.1)	14 (12.7)	0.2777
CA19-9 ≥ 300 U/ml	12 (31.6)	45 (40.5)	0.3223
CRP ≥ 1 mg/dl	14 (36.8)	0 (0)	< 0.001
Alb ≥ 3.5 g/dl	20 (52.6)	101 (91.0)	< 0.001
Fibrinogen ≥ 400	36 (94.7)	60 (54.1)	< 0.001
DP/PD/TP	8/28/2	38/70/3	0.2585
PV resection	9 (23.7)	14 (12.6)	0.1161
NAC	6 (15.8)	10 (9.1)	0.2686
AC	18 (47.4)	71 (64.0)	0.0737
T(3+4)	32 (84.2)	64 (62.2)	0.0087
N(+)	15 (40.5)	36 (33.3)	0.4296
LCR < 15090	35 (100)	36 (33.3)	< 0.001
NLR ≥ 3	21 (60)	33 (30.6)	0.0018
PNI < 45	10 (28.6)	77 (71.3)	< 0.001
PLR < 150	13 (37.1)	50 (46.3)	0.3432
mGPS 1,2	11 (28.9)	0 (0)	< 0.001

n (%)

DISCUSSION

In this study, OS and DFS were significantly worse in patients with resectable PDAC and a high CAR of >0.06. The CAR was an independent prognostic factor for OS and DFS in the multivariate analysis. To the best of our knowledge, no study has compared other prognostic markers such as lymphocyte to CRP ratio (LCR), NLR, PNI, PLR, and mGPS in patients with resectable PDAC.

In our study, the higher value of CAR was correlated with other prognostic markers which calculated with CRP and serum albumin and it was statistically superior to the other prognostic markers. The higher value of CAR was also correlated with higher T factor which reflected in local advancement of the pancreatic cancer.

The precise mechanism of the relation between the CAR and prognosis in patients with resectable PDAC has not been fully elucidated yet. Several possible mechanism has been reported in basic research articles. Mantovani A *et al*. reported that the migration, invasion, and metastasis of cancer cells could contribute to the inflammation through the activation of several chemokines such as CXCR4 and its ligand CXCL12 (19) ; as a result, the CRP reflects a cancer-specific inflammatory response to tumour necrosis or local tissue damage and indicates a favourable environment for the establishment and growth of distant metastasis. Yang J *et al*. also reported that CRP binding activated Fcγ receptors and stimulated the PI3K/AKT, ERK, and NFκB pathways and inhibited caspase cascade activation induced. CRP also enhanced myeloma cell secretion of IL-6 and IL-6-protected myeloma cells resulting from chemotherapy drug-induced apoptosis. Therefore CRP could be one of the candidate of new therapeutic approach for cancer in basic research (20).

On the other hand, serum albumin level is low in patients with PDAC especially in the perioperative period because of malnutrition and cachexia. Improvement of perioperative immune-nutritional status reduced post-operative inflammation (21, 22). Poor nutritional state in pancreatic surgery has been reported to be associated with worse postoperative survival (11). Therefore, the CAR calculated with two critical factors could represent the inflammation and nutritional status of PDAC patients.

Recently, CAR was also reported as one of the poor prognostic marker not only in solid cancer but also hematologic cancer such as malignant lymphoma (23). Moreover, Araki T *et al*. reported that evaluation of CAR could predict therapeutic response to immune check point inhibitor such as nivolumab (24).

There were several limitations to this study. This study was retrospective and the sample size was relatively small. Further studies using a larger sample size and a prospective approach or propensity score matching are required.

In conclusion, the preoperative CAR is a poor prognostic factor in patients with resectable PDAC. CAR can be simply calculated using preoperative serum CRP and albumin and reflects local inflammation caused by invasion of PDAC.

COMPETING INTERESTS

The authors declare that they have no competing interests

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