

High C-reactive protein/albumin ratio associated with reduced survival due to advanced stage of intrahepatic cholangiocarcinoma

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SUMMARY C-reactive protein (CRP)- and albumin (Alb)-based scoring systems are available for predicting the prognosis of patients with diverse forms of gastrointestinal cancer, but their utility for patients with intrahepatic cholangiocarcinoma (ICC) is still unclear. This study aimed to elucidate whether a high CRP/Alb ratio is associated with the surgical outcome of ICC patients. Patients who underwent initial and curative resection for ICC were included in this study, and were divided into the High and Low CRP/Alb groups based on their preoperative CRP and Alb values. The surgical outcomes were compared between the two groups. The median CRP/Alb ratio amongst 88 patients was 0.033 (range, 0.019-3.636); 44 patients with CRP/Alb > 0.033 were allocated to the High CRP/Alb group and 44 patients were allocated to the Low CRP/Alb group. The operative data did not differ between the two groups, while the tumor status was more advanced in the High CRP/Alb group. The median overall survival was 2.4 years (95% CI, 1.4-3.3) and 8.9 years (3.8-NA) in the High and Low CRP/Alb groups, respectively ($P < 0.001$), and recurrence-free survival was 0.5 years (95% CI, 0.3-0.7) and 7.7 years (1.3-NA), respectively ($P < 0.001$). In a multivariate analysis, the independent factors for overall survival were High CRP/Alb ($P = 0.017$) and multiple nodules ($P = 0.008$). Taken together, the survival of ICC patients in the High CRP/Alb group was reduced compared to that of patients in the Low CRP/Alb group due to the advanced stage of the tumor as well as malnutrition.

Keywords intrahepatic cholangiocarcinoma, C-reactive protein/albumin ratio, prognostic marker

1. Introduction

Both inflammation and nutrition-based prognostic systems such as the Glasgow prognostic score (GPS) and C-reactive protein/Albumin (CRP/Alb) ratio are brief and useful markers for surgical outcomes in patients with diverse forms of gastroenterological cancer, such as esophageal (1), gastric (2), colorectal (3,4), and pancreatic cancer (5,6). In primary liver cancer, high scores of GPS and CRP/Alb ratio have also been associated with reduced survival after operation in patients with hepatocellular carcinoma (7-9), although it is still unclear whether CRP/Alb ratio can predict survival in patients with intrahepatic cholangiocarcinoma (ICC) (10,11).

ICC makes up approximately 5% of all primary liver cancer cases, and prognosis is very poor because of the possibility of relapse both outside and inside the liver, even when a patient undergoes liver resection at an early stage (12,13). Therefore, stratification of ICC

patients based on the risk of recurrence would be helpful for identifying candidates for postoperative adjuvant therapy (14,15). In addition to clinicopathological findings (16,17) and surgical procedures (18,19), various types of predictive marker, such as aspartate aminotransferase/neutrophil ratio (20), platelet/lymphocyte ratio (21), albumin/gGTP ratio (22), and neutrophil/lymphocyte ratio (23), have been reported as being negatively associated with patient survival after resection of ICC.

In this study, we classified patients who underwent curative resection for ICC according to the prognostic system, CRP/Alb ratio, and compared their surgical outcomes. Then, we elucidated whether a high CRP/Alb ratio was associated with the survival of patients with ICC.

2. Materials and Methods

2.1. Patients

Patients undergoing curative liver resection for ICC from 2000 to 2018 at Nihon University Itabashi Hospital were included in this study; each participant provided written informed consent, and the institutional review board of Nihon University approved this study. All the patients were closely observed during each of their outpatient office visits. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

2.2. Classification

Patients with ICC, which was diagnosed by two pathologists with more than 5 years' experience in the field of liver pathology, were divided into the two classes based on the preoperative CRP/Alb ratio. The cut-off value was determined as the median, and those patients with a CRP/Alb ratio higher than the cut-off value were allocated to the High CRP/Alb group, and the other patients to the Low CRP/Alb group.

2.3. Surgical procedures

Liver resection was performed for all patients based on the criteria regarding the number of tumors and liver function (24). Transection of the liver was performed under ultrasonographic guidance using the clamp-crushing method and the inflow blood occlusion technique (25). Systemic lymph nodes dissection was not routinely performed; only those that were diagnosed as metastatic before or during operation were removed. Anatomic resection was defined as any type of systematic resection of the portal regions based on Couinaud's classification. Major liver resection was defined as resection of three or more segments. Curative resection was defined as the complete removal of recognizable viable ICC diagnosed preoperatively or intraoperatively with macroscopically tumor-free surgical margins.

2.4. Follow-up after operation

All patients were followed for postoperative recurrence as described previously (26). Briefly, tumor marker levels, including those of carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9), were measured, and imaging studies, including computed tomography and ultrasonography, were performed every three months in all patients. Recurrence was diagnosed by dynamic computed tomography and/or by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging, and 18F-fluorodeoxyglucose-positron emission tomography. The date of recurrence was defined as the date of examination when the recurrent ICC was noted.

2.5. Statistical analysis

Data collected from each group were statistically analyzed using Fisher's exact test and the Wilcoxon rank-sum test. Survival curves were generated using the Kaplan–Meier method and compared using the Wilcoxon test. Prognostic factors for survival were identified using the Cox proportional hazards regression model. A *P* value of less than 0.10 was set as the cut-off value for elimination. The following 11 variables, considered potential confounders, were examined: age (≥ 70 versus < 70 years), sex, positive for hepatitis B or C virus, indocyanine green clearance rate at 15 minutes (ICGR15) (≥ 15 versus $< 15\%$), frequency of esophageal varices, tumor size (≥ 5.0 versus < 5.0 cm), tumor number (single versus multiple), tumor thrombus, serum carcinoembryonic antigen level (≥ 5.0 versus < 5.0 ng/mL), CA19-9 level (≥ 37 versus < 37 ng/mL), and CRP/Alb ratio. In all analyses, a *P* value < 0.05 was considered to be statistically significant.

3. Results

3.1. Patients

The median CRP/Alb ratio amongst 88 patients who underwent initial and curative resection for ICC was 0.033 (range, 0.019-3.636), from whom 44 patients with a CRP/Alb ratio > 0.033 were allocated to the High CRP/Alb group (median, 0.139; range, 0.034-3.636), and 44 patients with a CRP/Alb ratio < 0.033 were allocated to the Low CRP/Alb group (median, 0.023; range, 0.019-0.032) (Figure 1).

Patient background did not differ between the two groups, except for CA 19-9, which was significantly higher in the High CRP/Alb group ($P = 0.005$) (Table 1).

3.2. Operative data

Operation data and postoperative complication rates did not differ between the two groups (Table 2). Two patients (for bile leakage and an intra-abdominal abscess) and one patient (for wound infection) underwent re-operation in the High and Low CRP/Alb groups, respectively, but

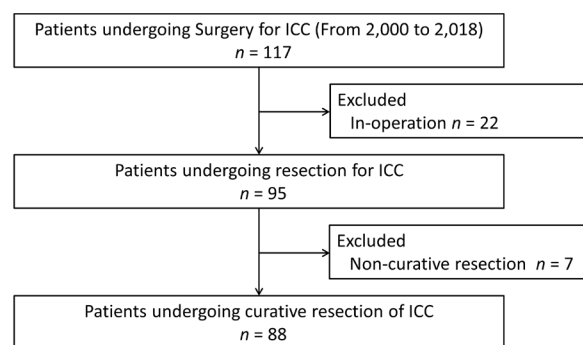


Figure 1. Flow diagram illustrating the recruitment of patients with ICC. ICC, intrahepatic cholangiocarcinoma.

Table 1. Patient background

Variables	High CRP/Alb (n = 44)	Low CRP/Alb (n = 44)	P value
Age, years	68 (23-84)	69 (41-84)	0.622
Sex, male (%)	28 (63.6)	33 (75.0)	0.355
Alcoholic, n (%)	8 (18.1)	9 (20.4)	1
Diabetes mellitus, n (%)	9 (20.4)	9 (20.4)	1
HBV, n (%)	1 (2.2)	7 (15.9)	0.057
HCV, n (%)	5 (11.3)	6 (13.6)	1
Varices, n (%)	2 (4.5)	1 (2.2)	1
Child-Pugh, A (%)	42 (95.4)	44 (100)	0.494
ICGR15, %	8.8 (1.9-26.8)	9.4 (2.0-33.4)	0.667
CEA, ng/mL	3.3 (0.2-175.1)	2.8 (0.4-71.5)	0.362
CA19-9, U/mL	82.8 (0.5-117800)	22.5 (0.1-39950)	0.005

Data are presented as median with range, if not specified. HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, indocyanine green clearance rate at 15 minutes; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 2. Operative data

Variables	High CRP/Alb (n = 44)	Low CRP/Alb (n = 44)	P value
Operation data			
Operation time, min	392 (168-869)	381 (170-795)	0.229
Bleeding, mL	326 (20-1,752)	352 (29-11,002)	0.442
Transfusion, n (%)	2 (4.5)	4 (9.0)	0.116
Major resection, n (%)	21 (47.7)	22 (50.0)	1
Anatomic resection, n (%)	35 (79.5)	29 (65.9)	0.231
Complications			
Overall, n (%)	19 (43.1)	11 (25.0)	0.114
Morbidity, n (%)	10 (22.7)	8 (18.1)	0.792
Re-operation, n (%)	2 (4.5)	1 (2.2)	1
Mortality, n (%)	0	0	1
Pathology			
Multiple, n (%)	15 (34.0)	5 (11.3)	0.020
Size, cm (range)	5.2 (1.8-12.3)	3.4 (1.0-10.5)	0.001
Differentiation grade, mod, (%)	39 (88.6)	41 (93.1)	0.713
Vascular invasion, n (%)	32 (72.7)	20 (47.7)	0.026
Tumor exposure, n (%)	11 (25.0)	5 (11.3)	0.165
Cirrhosis	2 (4.5)	3 (6.8)	1

Data are presented as median, if not specified.

there was no in-hospital death in this series. Histological findings for the resected specimens showed that tumor status was more advanced in the High CRP/Alb group; multiple nodules ($P = 0.020$) and vascular invasion ($P = 0.026$) were more frequent, and tumor size was larger ($P = 0.001$), in the High CRP/Alb group.

3.3. Survival

After a median follow-up of 1.4 years (range, 0.3 to 10.3 years), a total of 48 patients (54.5%) experienced recurrence; 28 patients (58.3%) in the remnant liver, 11 patients (12.5%) in distant sites, and nine patients with both intra- and extra-hepatic recurrences (Table 3). Extrahepatic recurrence was more frequent in the Low CRP/Alb group (30.3% vs 66.6%, $P = 0.027$). Treatment for recurrent ICC did not differ between the two groups.

Median overall survival was 2.4 years (95% confidence interval [CI], 1.4-3.3) and 8.9 years (3.0-NA; $P < 0.001$) in the High CRP/Alb and the Low CRP/Alb groups, respectively (Figure 2A), and recurrence-free survival was 0.5 years (95% CI, 0.3-0.7) and 7.7 years

Table 3. Treatment for recurrence

Variables	High CRP/Alb (n = 33)	Low CRP/Alb (n = 15)	P value
Recurrent sites			
Intrahepatic	23 (69.6)	5 (33.3)	0.004
Distant sites	3 (9.0)	8 (53.3)	
Both	7 (21.2)	2 (13.3)	
Treatments			
Second resection	5 (15.1)	2 (13.3)	0.410
TACE/TAI	9 (27.2)	1 (6.6)	
Chemotherapy	12 (36.3)	8 (24.2)	
Radiation therapy	4 (12.1)	1 (6.6)	
None	3 (9.0)	3 (20.0)	

Data are presented as median with range, if not specified. TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion.

(1.3-NA; $P < 0.001$), respectively (Figure 2B). The 5-year rate of overall survival was 19.1% and 65.0%, and that of recurrence-free survival was 14.4% and 55.9% in the two groups, respectively.

In a multivariate analysis, the independent factors

affecting overall survival were High CRP/Alb (hazard ratio [HR], 2.82, 95% CI, 1.20-7.17; $P = 0.017$) and the presence of multiple nodules (HR, 3.98, 95% CI, 1.42-11.09; $P = 0.008$) (Table 4). The independent factors affecting recurrence were High CRP/Alb ratio (HR, 3.28, 95% CI, 1.64-6.80; $P < 0.001$) and the presence

of multiple nodules (HR, 7.67, 95% CI, 3.57-16.50; $P < 0.001$) (Table 5).

4. Discussion

We demonstrate that a high preoperative CRP/Alb ratio is related to advanced tumor stage and reduced survival in patients with ICC. This is the first report showing the utility of a scoring system based on inflammation and nutritional status (CRP/Alb ratio) for stratifying patients after resection of ICC.

GPS was originally proposed as a prognostic marker for patients with non-small lung cell cancer, which was superior to clinical stage or performance status (27). It was later shown that GPS reflected malnutrition status based on the systemic inflammation response, "cancer cachexia" (28). Given that many ICC patients experience early recurrence even after curative resection, it is possible that patient survival is longer in our Low CRP/Alb group, and in the GPS-Low group in the Pan *et al.* (11) study, due to the possible continuation of cancer treatments for recurrent tumors, including chemotherapy, radiation therapy, transcatheter arterial chemoembolization, and infusion.

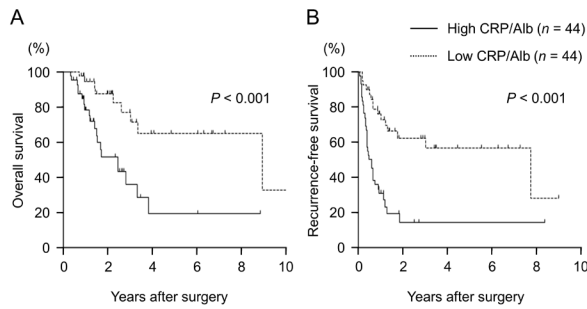


Figure 2. Surgical outcomes of patients undergoing resection for ICC. (A) Overall survival of patients in the High CRP/Alb group is significantly less than that of patients in the Low CRP/Alb group ($P = 0.001$). (B) Recurrence-free survival of patients in the High CRP/Alb group is significantly less than that of patients in the Low CRP/Alb group ($P < 0.001$). CRP, C-reactive protein; Alb, albumin; ICC, intrahepatic cholangiocarcinoma.

Table 4. Prognostic factors for survival

Variables	Univariate		Multivariate	
	Hazard ratio	P value	Hazard ratio	P value
Age	1.02 (0.47-2.17)	0.958		
Sex	1.19 (0.53-2.52)	0.657		
Viral hepatitis	0.79 (0.26-1.93)	0.635		
ICGR15	1.08 (0.46-2.94)	0.864		
Varices	0.92 (0.33-2.15)	0.864		
Size	2.59 (1.23-5.47)	0.012	1.37 (0.56-3.24)	0.477
Multiple	6.45 (2.56-15.73)	< 0.001	3.98 (1.42-11.09)	0.008
Tumor Thrombus	1.87 (0.87-4.24)	0.106		
CEA	0.74 (0.27-1.72)	0.511		
CA19-9	0.98 (0.45-2.08)	0.965		
CRP/Alb ratio	3.76 (1.70-9.16)	< 0.001	2.82 (1.20-7.17)	0.017

ICGR15, indocyanine green clearance rate at 15 minutes; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 5. Prognostic factors for recurrence

Variables	Univariate		Multivariate	
	Hazard ratio	P value	Hazard ratio	P value
Age	0.73 (0.40-1.30)	0.293		
Sex	1.14 (0.62-2.22)	0.666		
Viral hepatitis	0.56 (0.24-1.15)	0.123		
ICGR15	0.68 (0.29-1.39)	0.310		
Varices	1.59 (0.25-5.18)	0.548		
Size	2.09 (1.17-3.70)	0.012	1.12 (0.57-2.14)	0.727
Multiple	8.40 (4.25-16.36)	< 0.001	7.67 (3.57-16.50)	< 0.001
Tumor Thrombus	1.85 (1.03-3.43)	0.038	1.19 (0.61-2.38)	0.603
CEA	1.08 (0.55-1.98)	0.809		
CA19-9	1.49 (0.83-2.68)	0.174		
CRP/Alb ratio	3.81 (2.07-7.35)	< 0.001	3.28 (1.64-6.80)	< 0.001

ICGR15, indocyanine green clearance rate at 15 minutes; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

It has been reported that GPS and CRP/Alb ratio are positively associated with primary liver cancer progression; tumor stage is more advanced in patients with a higher GPS (7,11) and CRP/Alb ratio (8,9). Consequently, both overall and recurrence-free survival of patients in these studies were without exception significantly reduced in the high GPS and CRP/Alb ratio groups. Consistent with this, tumor status was more advanced in the High CRP/Alb group in our study; multiple tumors and vascular invasion were more frequent, tumors were larger, and serum CA19-9 levels were higher. Given that liver function, indicated by variables such as frequency of varices, Child-Pugh classification, and ICGR15, did not differ between the two groups, we attributed reduced survival in patients from the High/CRP group to the advanced stage of the tumor and the poor nutritional status of patients with a cancer burden.

In the studies reported above, cut-off values for the CRP/Alb ratio were determined using area under the curve of receiver operating characteristic curves (9) or X-tile plots (8), or were defined as the median value (10), and its range was from 0.024 to 0.033. Given that cut-off values for CRP/Alb ratio were from 0.018 to 0.10 for the other types of gastroenterological cancer (1-3,5,6), the value of 0.033 used in this study was appropriate.

There are several limitations of this study. First, tumor status was more advanced in the High CRP/Alb group, as in previous reports. Consequently, progressive cancer greatly influenced surgical outcomes and it is not yet clear whether nutritional status can contribute to the improvement of post-operational patient survival. In order to elucidate the relationship between nutritional status and survival, surgical outcomes should be compared after matching patient background and tumor stage between the two groups, using a much larger cohort. Second, the presence of any causal relationship between high CRP/Alb ratio and tumor progression remains unknown. Given that tumor status is more advanced in high GPS and high CRP/Alb ratio groups in previous primary liver cancer studies (7-9,11), we speculate that the deviation of tumor progression in the High CRP/Alb group in this study is not accidental, which needs to be clarified in the future.

In conclusion, survival of ICC patients in the High CRP/Alb group was significantly less than that of patients in the Low/CRP group. This is partly because the nutritional status of high CRP/Alb ratio patients negatively affected survival, but mainly because CRP/Alb ratio is associated with tumor progression, which dictated surgical outcome in patients with ICC.

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