Original article

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C-reactive protein : albumin ratio in patients with resectable intrahepatic cholangiocarcinoma

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Background: **The C-reactive protein : albumin ratio (CAR) has been reported as a novel prognostic marker in several cancers. The aim of this study was to investigate the prognostic value of CAR in patients with intrahepatic cholangiocarcinoma (ICC).**

Methods: **This was a single-centre retrospective study of patients who underwent surgery for ICC in a university hospital in Japan between 1998 and 2018. CAR, Glasgow Prognostic Score (GPS) and modified GPS (mGPS) were calculated. Their correlation with recurrence-free survival (RFS) and overall survival (OS) was analysed with Cox proportional hazards models.**

Results: **Seventy-two patients were included in the study. Patients were divided into two groups according to the optimal CAR cut-off value of 0·02. CAR above 0·02 was associated with higher carbohydrate antigen 19-9 levels (20·5 *versus* 66·1 units/ml for CAR of 0·02 or less; $P = 0·002$), larger tumour size (3·2 *versus* 4·4 cm respectively; $P = 0·031$) and a higher rate of microvascular invasion (9 of 28 *versus* 25 of 44; $P = 0·041$). RFS and OS were shorter in patients with CAR above 0·02: hazard ratio (HR) 4·31 (95 per cent c.i. 2·02 to 10·63) and HR 4·80 (1·85 to 16·40) respectively. In multivariable analysis CAR above 0·02 was an independent prognostic factor of RFS (HR 3·29 (1·33 to 8·12); $P < 0·001$), but not OS.**

Conclusions: **CAR was associated with prognosis in patients who had hepatic resection for ICC.**

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma[1]. Its incidence is increasing worldwide, and patients with ICC have poorer prognosis than those with most other cancers. The 5-year survival rate among patients with ICC is only 3–31 per cent as a result of several frequently occurring factors, including lymph node involvement, intrahepatic metastasis and refractoriness to chemotherapy[2–4]. Management of advanced ICC is therefore shifting towards multidisciplinary approaches in an attempt to improve patients' prognosis. Surgical resection is considered the only curative treatment for ICC at present.

Preoperative prediction of a patient's prognosis using reliable biomarkers is important for offering appropriate treatment and postoperative follow-up strategies. Some studies[5,6] have demonstrated that tumour markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 are prognostic factors associated with poor prognosis after surgery. In addition, cancer-related inflammation is associated with tumour cell survival, proliferation and metastasis[7,8]. Biomarkers for cancer-related inflammation, such as the preoperative neutrophil : lymphocyte ratio and platelet : lymphocyte ratio, and biomarkers for nutrition, such as the Prognostic Nutritional Index and Controlling Nutritional Status score, are currently some of the strongest prognostic factors after curative resection for ICC[9–11].

The Glasgow Prognostic Score (GPS) is based on serum C-reactive protein (CRP) and albumin levels. The CRP level reflects inflammation, and the serum albumin level reflects nutritional condition. The CRP : albumin ratio (CAR) has recently been associated with poor outcomes in patients with acute medical admission and sepsis[12,13]. The CAR has been reported as a novel inflammation-based prognostic marker in multiple types of tumour[14–18]. The significance of CAR in patients with ICC remains unclear. The aim of this study was to investigate the relationship between CAR and prognosis in patients with ICC who underwent hepatectomy with curative intent.

Methods

This was a single-centre retrospective study performed at the Department of Surgery and Science, Kyushu University, Japan. All patients with ICC who had surgical resection between May 1998 and November 2018 were eligible. Exclusion criteria were a macroscopically unresectable tumour or insufficient clinical, surgical or pathology data in the patient's records.

Major hepatic resection with bile duct resection was performed when bile duct invasion by ICC was suspected to affect the first branch of the hepatic duct. Partial hepatic resection was performed in patients with peripheral ICC. If the surgical margin was suspected to be infiltrated by carcinoma cells, the resected stump was sent to the pathology department for frozen sectioning. Lymph node dissection was performed if lymph node metastasis was suspected on preoperative abdominal CT or during surgery[19].

The indication for adjuvant chemotherapy with gemcitabine or S-1 was determined by each physician in charge based on the patient's activities of daily life and the reported presence or absence of poor prognostic factors, such as lymph node metastasis, microscopic vascular invasion, microscopic intrahepatic metastasis and poor differentiation[2].

Patients were followed up with measurement of CEA or CA19-9 levels, as well as dynamic CT performed by radiologists every 3 months after hospital discharge. When recurrence was suspected, additional examinations, such as MRI, were performed as indicated.

This study was approved by the ethics committee of Kyushu University (approval code 30-455).

Outcomes

GPS, modified GPS (mGPS) and CAR for all patients in the study were calculated using preoperative blood samples. GPS and mGPS were calculated as described previously[20,21]. Briefly, for GPS, patients with both a CRP level above 1·0 mg/dl and an albumin concentration below 3·5 g/dl were assigned a score of 2; patients with only one of these abnormalities were assigned a score of 1; and patients with neither of these abnormalities were assigned a score of 0. For mGPS, patients were assigned a score of 0, 1 or 2 based on serum CRP and albumin levels (0: CRP 1·0 mg/dl or less; 1: CRP above 1·0 mg/dl and albumin 3·5 g/dl or more; 2: CRP above 1·0 mg/dl and albumin below 3·5 g/dl). CAR was defined as the serum CRP level divided by the serum albumin level[15]. The best cut-off values for these markers were determined by the receiver operating characteristic (ROC) curve.

The main outcome of this study was survival.

Statistical analysis

Data are expressed as median (range) values. Continuous variables with a non-normal distribution were compared by the Mann–Whitney *U* test. Categorical variables, including sex, tumour differentiation, microscopic vascular invasion, microscopic bile duct metastasis, curability, adjuvant chemotherapy and period, were compared between groups using the χ^2 test, and hepatitis virus, lymph node metastasis and macroscopic liver cirrhosis were compared with Fisher's exact test. Recurrence-free survival (RFS) and overall survival (OS) were calculated by the Kaplan–Meier method and compared with the log rank test. Co-variables that differed significantly in univariable analysis were included in a multivariable Cox proportional hazards model. Differences were considered significant at $P < 0{\cdot}050$. All statistical analyses were performed using JMP® software (SAS Institute, Cary, North Carolina, USA).

Results

A total of 72 patients (49 men and 23 women) with a median age of 66 years were included in this study. Clinicopathological characteristics of patients with a high and low CAR are shown in *Table 1*.

The best cut-off value of CAR for postoperative prognosis was determined using ROC curves (*Fig. 1*). The best cut-off point for CAR was 0·02, and the area under the ROC curve was 0·727. CAR correlated with serum albumin ($P = 0{\cdot}020$), CRP ($P < 0{\cdot}001$) and CA19-9 ($P = 0{\cdot}002$) levels. Tumour size was larger ($P = 0{\cdot}031$) and presence of microvascular invasion more frequent ($P = 0{\cdot}041$) in patients with a high CAR.

Of the 72 patients, 62 (86 per cent) had a preoperative GPS of 0, nine (13 per cent) had a GPS of 1, and one

Table 1 Clinicopathological characteristics of patients with intrahepatic cholangiocarcinoma who had hepatic resection

	CAR ≤ 0·02 (*n* = 28)	CAR > 0·02 (*n* = 44)	*P*†
Age (years)*	66 (41–87)	66·5 (39–87)	0·799§
Sex ratio (M : F)	18 : 10	31 : 13	0·584
HBsAg-positive	2	6	0·471‡
HCV Ab-positive	5	3	0·248‡
Albumin (g/dl)*	4·2 (3·6–4·9)	4·0 (3·3–5·3)	0·020§
Total bilirubin (mg/dl)*	0·7 (0·2–1·6)	0·7 (0·3–8·7)	0·894§
CRP (mg/dl)*	0·06 (0·01–0·09)	0·3 (0·09–4·01)	< 0·001§
Total no. of lymphocytes (cells/μl)*	1520 (363–2490)	1439 (699–3950)	0·799§
Platelets (× 10^4/μl)*	16·9 (8·3–40·2)	19·5 (5·2–44·0)	0·135§
CA19-9 (units/ml)*	20·5 (0·6–293·7)	66·1 (0·6–40 795)	0·002§
Tumour size (cm)*	3·2 (1·6–7·5)	4·4 (0·5–12)	0·031§
Tumour localization			0·137
Peripheral type	25	32	
Hilar type	3	12	
Poor differentiation	19	23	0·191
Microscopic vascular invasion	9	25	0·041
Microscopic bile duct invasion	10	21	0·316
Lymph node metastasis	3	11	0·222‡
Microscopic liver cirrhosis	3	6	0·715‡
R0 resection	22	34	0·897
Adjuvant chemotherapy	11	8	0·048
Time interval			0·094
1998–2008	9	23	
2009–2018	19	21	

*Values are median (range). CAR, C-reactive protein : albumin ratio; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; CRP, C-reactive protein; CA, carbohydrate antigen. †χ^2 test, except ‡Fisher's exact test and §Mann–Whitney *U* test.

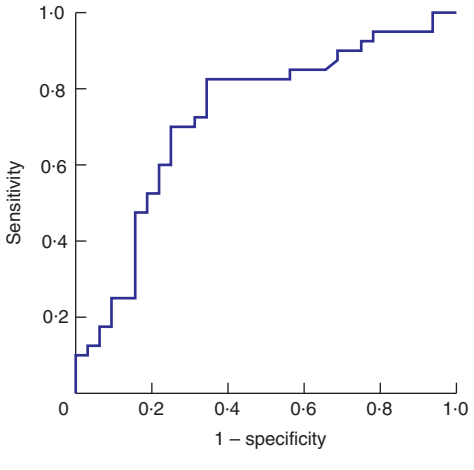
(1 per cent) had a GPS of 2. Sixty-three patients (88 per cent) had a preoperative mGPS of 0, eight (11 per cent) had an mGPS of 1, and one (1 per cent) had a mGPS of 2.

Survival

Median follow-up was 2·2 (range 0·1–16·6) years. The number of patients who had postoperative adjuvant chemotherapy was lower in patients with a high CAR ($P = 0·048$) (*Table 1*).

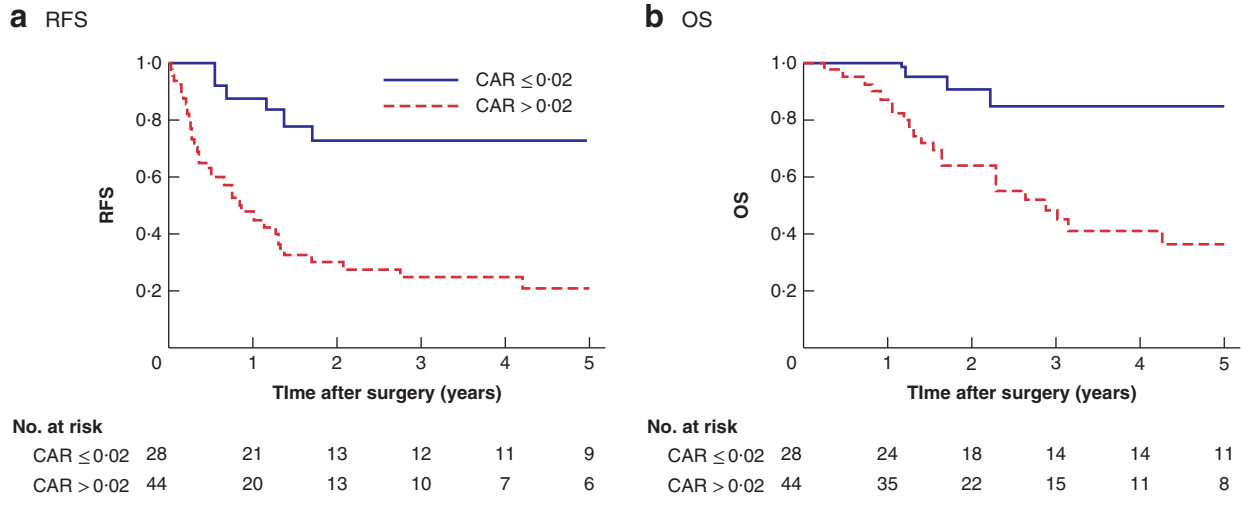
RFS and OS curves after hepatic resection for ICC are shown in *Fig. 2*. RFS in the high CAR group was lower than that in low CAR group (hazard ratio (HR) 4·31 (95 per cent c.i. 2·02 to 10·63); $P < 0·001$) (*Table 2*). The 1-, 3- and 5-year RFS rates in the high *versus* low CAR group were 47 *versus* 88, 24 *versus* 72, and 20 *versus* 72 per cent respectively. OS was lower in the high CAR group (HR 4·80 (1·85 to 16·40); $P < 0·001$) (*Table 3*). The 1-, 3- and 5-year OS rates in the high *versus* low CAR group were 87 *versus* 100, 48 *versus* 84, and 37 *versus*

Fig. 1 Receiver operating characteristic (ROC) curve using C-reactive protein : albumin ratio as a predictor of overall survival after hepatic resection with an optimal cut-off value of 0·20



The area under the ROC curve was 0·727.

Fig. 2 Kaplan–Meier curves of recurrence-free and overall survival after hepatic resection for intrahepatic cholangiocarcinoma in patients with a high *versus* low C-reactive protein : albumin ratio



a Recurrence-free survival (RFS) and **b** overall survival (OS). CAR, C-reactive protein : albumin ratio. **a,b** $P < 0{\cdot}001$ (log rank test).

Table 2 Univariable and multivariable Cox proportional hazards analysis of factors related to recurrence-free survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Age (≥ 60 years)	1·13 (0·59, 2·24)	0·720		
Male sex	1·19 (0·62, 2·44)	0·605		
CA19-9 (≥ 37·0 units/ml)	2·07 (1·10, 4·04)	0·024	0·80 (0·35, 1·82)	0·592
Tumour size (≥ 3·0 cm)	3·08 (1·38, 8·21)	0·005	2·29 (0·80, 6·52)	0·121
Hilar type	3·33 (1·66, 6·43)	0·001	2·89 (1·17, 7·13)	0·021
Poor differentiation	1·20 (0·64, 2·28)	0·571		
Microscopic vascular invasion	2·52 (1·32, 5·00)	0·005	1·24 (0·58, 2·65)	0·582
Microscopic bile duct invasion	1·33 (0·71, 2·50)	0·370		
Lymph node metastasis	2·31 (1·12, 4·47)	0·024	0·95 (0·42, 2·15)	0·900
Microscopic liver cirrhosis	1·04 (0·31, 2·62)	0·940		
Adjuvant chemotherapy	0·51 (0·22, 1·07)	0·075		
GPS score 1 or 2	2·05 (0·87, 4·28)	0·095		
mGPS score 1 or 2	1·75 (0·77, 3·99)	0·185		
CAR > 0·02	4·31 (2·02, 10·63)	< 0·001	3·29 (1·33, 8·12)	< 0·001

Values in parentheses are 95 per cent confidence intervals. CA, carbohydrate antigen; (m)GPS, (modified) Glasgow Prognostic Score; CAR, C-reactive protein : albumin ratio.

84 per cent respectively. In contrast, GPS and mGPS were not associated with a poor prognosis in patients with ICC who underwent hepatic resection (*Tables 2* and *3*).

Factors associated with RFS in univariable analysis were CA19-9 level, hilar type, tumour size, microvascular invasion, lymph node metastasis and CAR (*Table 2*). In multivariable analysis, hilar type and high CAR were found to be poor prognostic factors for RFS. Factors associated with OS in univariable analysis were CA19-9 level, hilar type, tumour size, microvascular invasion, lymph node metastasis and CAR (*Table 3*). Hilar type was the only independent prognostic factor of OS in multivariable analysis.

Table 3 Univariable and multivariable Cox proportional hazards analysis of factors related to overall survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Age (≥ 60 years)	1·75 (0·80, 4·16)	0·166		
Male sex	1·06 (0·49, 2·47)	0·881		
CA19-9 (≥ 37·0 units/ml)	4·19 (1·86, 10·69)	< 0·001	2·41 (0·90, 6·46)	0·079
Tumour size (≥ 3·0 cm)	2·91 (1·12, 9·97)	0·027	1·73 (0·47, 6·37)	0·408
Hilar type	5·59 (2·54, 12·21)	< 0·001	3·85 (1·46, 10·10)	0·006
Poor differentiation	1·02 (0·48, 2·18)	0·960		
Microscopic vascular invasion	2·20 (1·01, 5·16)	0·048	1·06 (0·40, 2·80)	0·903
Microscopic bile duct invasion	2·06 (0·97, 4·64)	0·061		
Lymph node metastasis	4·14 (1·85, 8·90)	< 0·001	2·02 (0·80, 5·10)	0·138
Microscopic liver cirrhosis	1·15 (0·27, 3·28)	0·827		
Adjuvant chemotherapy	0·65 (0·24, 1·52)	0·332		
GPS score 1 or 2	2·07 (0·76, 4·82)	0·144		
mGPS score 1 or 2	2·08 (0·84, 5·15)	0·114		
CAR > 0·02	4·80 (1·85, 16·40)	< 0·001	2·33 (0·70, 7·74)	0·166

Values in parentheses are 95 per cent confidence intervals. CA, carbohydrate antigen; (m)GPS, (modified) Glasgow Prognostic Score; CAR, C-reactive protein : albumin ratio.

Discussion

This study has shown that high CAR is independently associated with RFS in patients with ICC. Patients with a high CAR had more aggressive tumour behaviour, including larger tumour size, higher frequency of microvascular invasion and higher serum CA19-9 concentration, than patients with a low preoperative CAR.

CAR has not yet been widely investigated as a prognostic indicator in patients with ICC. There is no unified standard concerning the optimal cut-off value for the CAR. Therefore, ROC curve analysis was performed in the present study, and 0·02 was defined as the best cut-off value. This cut-off value should be confirmed in a larger study.

CRP configuring CAR and GPS is an acute-phase protein (APP) produced in the liver, and its upregulation is controlled by cytokines such as interleukin (IL) 6, IL-8 and tumour necrosis factor α[22]. Thus, increased CRP levels in patients with advanced cancer may reflect raised cytokine levels. Among the various markers of inflammation, CRP is an acute-phase reactant that is synthesized by hepatocytes and regulated by proinflammatory cytokines, particularly IL-6[23]. *In vivo* studies have shown that IL-6 is an autocrine growth factor in cholangiocarcinoma cell lines[24]. Lack of serum IL-6 level measurement was a limitation of the present study. This mechanism reflects the serum IL-6 and CRP levels in patients with cancer. Chronic rise of CRP reflected the rise of IL-6 which is the extent of inflammation in the patients with cancer. Increased IL-6 level reflects the movement of APPs. CRP is representative of increasing APPs, whereas serum albumin is representative of decreasing APPs. Thus, CAR is a scoring indicator of the movement of APPs. CAR may conceal the individual factors, and instead more strongly emphasize the merit of each parameter in both inflammation and nutrition compared with other inflammatory or nutritional factors.

The present study suggests that the CAR may be superior to the GPS and mGPS in terms of its ability to serve as an inflammatory and nutritional prognostic marker. GPS and mGPS are outstanding prognostic scores in various cancers[21,25]. In the present study, only two patients had a serum albumin level below 3·5 g/dl; therefore, a low number of patients had a high GPS or mGPS (score of 1 or 2). In such a patient group, these scores are of limited value.

Low CAR was not an independent prognostic factor of OS. Hilar type was an independent unfavourable predictor of RFS and OS in patients with ICC. It might be possible that this factor diminished the potential effect of CAR.

The clinical consequence of a high CAR in ICC is unclear. Median OS in patients with high CAR in resectable ICC was 34 months, compared with only about 12 months in patients with unresectable ICC[4,26]. Surgical treatment is beneficial for resectable ICC compared with alternative treatments. The present authors suggest that adjuvant or neoadjuvant chemotherapy be considered in patients with a high CAR and resectable ICC, but the value of systemic treatment in these patients should be explored.

This study has several limitations, including its design, small sample size and long time interval. A larger validation study is required to confirm these findings.

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