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.

Funding information
Japan Society for the Promotion of Science, JP-16K10576, 19K09198

Paper accepted 15 July 2020
Published online 21 September 2020 in Wiley Online Library (www.bjsopen.com). DOI: 10.1002/bjs5.50348

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma1. 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 chemotherapy2–4. 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 studies5,6 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 metastasis7,8. 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 ICC9–11.
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\(^9\).

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 \(\chi^2\) 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 \(P<0·050\). All statistical analyses were performed using JMP\(^\text{®}\) 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 \((P = 0·020)\), CRP \((P < 0·001)\) and CA19-9 \((P = 0·002)\) levels. Tumour size was larger \((P = 0·031)\) and presence of microvascular invasion more frequent \((P = 0·041)\) 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...
(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

---

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

| Characteristic                        | 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 (0.6–40795)    | 0.002§  |
| Tumour size (cm)*                    | 3.2 (1.6–7.5)       | 4.4 (0.5–12)        | 0.031§  |
| Tumour localization                  |                     |                     |         |
| 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.

---

**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. 

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

| Factor                                      | Univariable analysis | Multivariable analysis |
|---------------------------------------------|----------------------|------------------------|
| 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                  |
| Tumour size (≥3.0 cm)                       | 3.08 (1.38, 8.21)    | 0.005                  |
| Hilar type                                  | 3.33 (1.66, 6.43)    | 0.001                  |
| Poor differentiation                        | 1.20 (0.64, 2.28)    | 0.571                  |
| Microscopic vascular invasion               | 2.52 (1.32, 5.00)    | 0.005                  |
| Microscopic bile duct invasion              | 1.33 (0.71, 2.50)    | 0.370                  |
| Lymph node metastasis                       | 2.31 (1.12, 4.47)    | 0.024                  |
| Microscopic liver cirrhosis                | 1.04 (0.31, 3.62)    | 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                 |
| CAR > 0.02                                  | 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.
cytes and regulated by proinflammatory cytokines, partic-
is an acute-phase reactant that is synthesized by hepato-
levels. Among the various markers of inflammation, CRP
patients with advanced cancer may reflect raised cytokine
autocrine growth factor in cholangiocarcinoma cell lines.\(^2\)

CRP configuring CAR and GPS is an acute-phase pro-
tein: albumin ratio.

**Discussion**

This study has shown that high CAR is independently asso-
ciated with RFS in patients with ICC. Patients with a high
CAR had more aggressive tumour behaviour, including
larger tumour size, higher frequency of microvascular inva-
sion 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. There-
fore, 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 pro-
tein (APP) produced in the liver, and its upregulation is
controlled by cytokines such as interleukin (IL) 6, IL-8 and
tumour necrosis factor \(\alpha\). 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 hepato-
cytes and regulated by proinflammatory cytokines, partic-
ularly IL-6.\(^2\) In \textit{vivo} studies have shown that IL-6 is an
autocrine growth factor in cholangiocarcinoma cell lines.\(^2\)
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 representa-
tive 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 com-
pared 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.\(^2\) 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.\(^2\) 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.

Acknowledgements

The authors thank A. Morben from the Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

The study was supported by the Japan Society for the Promotion of Science, a Grant-in-Aid from the Ministry of Health, Labour and Welfare, Japan (numbers JP-16K10576 and 19K09198). The funding source had no role in the collection, analysis or interpretation of the data, or in the decision to submit the article for publication.

Disclosure: The authors declare no conflict of interest.

References

1 Khan SA, Emadossadaty S, Ladep NG, Thomas HC, Elliott P, Taylor-Robinson SD et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 2012; 56: 848–854.

2 Yamashita YI, Shirabe K, Beppu T, Eguchi S, Nanashima A, Ohta M et al. Surgical management of recurrent intrahepatic cholangiocarcinoma: predictors, adjuvant chemotherapy, and surgical therapy for recurrence: a multi-institutional study by the Kyushu Study Group of Liver Surgery. Ann Gastroenterol Surg 2017; 1: 136–142.

3 de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 2011; 29: 3140–3145.

4 Valle J, Wasan H, Palmer DH, Cunningham D, Anthonhey A, Maraveyas A et al.; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine to sterilize biliary tract cancer. N Engl J Med 2010; 362: 1273–1281.

5 Harada N, Yoshizumi T, Yamashita YI, Soejima Y, Ikegami T, Harimoto N et al. Impact and prediction of lymph node involvement in patients with intrahepatic cholangiocarcinoma after curative resection. Anticancer Res 2017; 37: 3763–3769.

6 Ohtsuka M, Ito H, Kimura F, Shimizu H, Togawa A, Yoshidome K et al. Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. Br J Surg 2002; 89: 1525–1531.

7 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646–674.

8 Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008; 454: 436–444.

9 Okuno M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T et al. Evaluation of inflammation-based prognostic scores in patients undergoing hepatobiliary resection for perihilar cholangiocarcinoma. J Gastroenterol 2016; 51: 153–161.

10 Zhang C, Wang H, Ning Z, Xu L, Zhuang L, Wang P et al. Prognostic nutritional index serves as a predictive marker of survival and associates with systemic inflammatory response in metastatic intrahepatic cholangiocarcinoma. Onco Targets Ther 2016; 9: 6417–6423.

11 Miyata T, Yamashita YI, Higashi T, Taki K, Izumi D, Kosumi K et al. The prognostic impact of controlling nutritional status (CONUT) in intrahepatic cholangiocarcinoma following curative hepatectomy: a retrospective single institution study. World J Surg 2018; 42: 1085–1091.

12 Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med 2009; 9: 30–33.

13 Ranzoni OT, Zampieri FG, Forte DN, Azevedo LC, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One 2013; 8: e59321.

14 Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol 2015; 22: 803–810.

15 Ishizuka M, Nagata H, Tåkagi K, Iwasaki Y, Shibuya N, Kubota K. Clinical significance of the C-reactive protein to albumin ratio for survival after surgery for colorectal cancer. Ann Surg Oncol 2016; 23: 900–907.

16 Xu XL, Yu HQ, Hu W, Song Q, Mao WM. A novel inflammation-based prognostic score, the C-reactive protein/albumin ratio predicts the prognosis of patients with operable esophageal squamous cell carcinoma. PLoS One 2015; 10: e0138657.

17 Kudou K, Saeki H, Nakashima Y, Kamori T, Kawaoe T, Haruta Y et al. C-reactive protein/albumin ratio is a poor prognostic factor for esophagogastric junction and upper gastric cancer. J Gastroenterol Hepatol 2019; 34: 355–363.

18 Arima K, Yamashita YI, Hashimoto D, Nakagawa S, Umezaki N, Yamao Y et al. Clinical usefulness of postoperative C-reactive protein/albumin ratio in pancreatic ductal adenocarcinoma. Am J Surg 2018; 216: 111–115.

19 Yagawa K, Itoh S, Kurihara T, Yoshiya S, Mano Y, Takeishi K et al. Skeletal muscle mass predicts the prognosis of patients with intrahepatic cholangiocarcinoma. Am J Surg 2019; 218: 952–958.

20 Forrest LM, McIllan DC, Mc Ardle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 2003; 89: 1028–1030.

21 Proctor MJ, Morrison DS, Talwar D, Balmer SM, O’Reilly DS, Foulis AK et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer 2011; 104: 726–734.
22 Castell JV, Gómez-Lechón MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. *Hepatology* 1990; **12**: 1179–1186.

23 Morris-Stiff G, Gomez D, Prasad KR. C-reactive protein in liver cancer surgery. *Eur J Surg Oncol* 2008; **34**: 727–729.

24 Okada K, Shimizu Y, Nambu S, Higuchi K, Watanabe A. Interleukin-6 functions as an autocrine growth factor in a cholangiocarcinoma cell line. *J Gastroenterol Hepatol* 1994; **9**: 462–467.

25 McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013; **39**: 534–540.

26 Bupathi M, Ahn DH, Bekaii-Saab T. Therapeutic options for intrahepatic chaolangiocarcinoma. *Hepatobiliary Surg Nutr* 2017; **6**: 91–100.