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Clinical Usefulness of Perioperative C-reactive Protein/Albumin Ratio in Patients With Intrahepatic Cholangiocarcinoma: A Retrospective Single Institutional Study

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Abstract. *Background/Aim: Prognoses of patients with cancer can be predicted on the basis of preoperative nutrition- or inflammation-based scores; however, predicting the prognostic impact of undergoing surgery remains challenging. In this study, we investigated the usefulness of the perioperative C-reactive protein/albumin (CRP/Alb) ratio in patients with intrahepatic cholangiocarcinoma (ICC). Patients and Methods: We retrospectively investigated 80 patients who had undergone curative resection of primary ICC between April 2002 and December 2017. We identified the time at which perioperative CRP/Alb ratio most influences the prognosis, and investigated the correlations among the perioperative CRP/Alb ratio, clinicopathological features and patient outcomes. Results: The only perioperative CRP/Alb ratios significantly associated with shorter overall survival (OS) was a high CRP/Alb ratio on POD14. High CRP/Alb ratio on POD 14 was significantly associated with older age, male sex, and the presence of postoperative complications. Finally, a high CRP/Alb ratio at POD 14 was an independent prognostic factor for poor OS. Conclusion: CRP/Alb ratio on POD 14 may be a useful prognostic factor in patients with ICC who have undergone curative resections.*

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma (HCC) (1). Although the incidence of ICC is increasing in the world, patients with ICC still have a poor prognosis, when compared to other cancers. The 5-year survival rate is only 3-31% because of frequent lymph node involvement, intrahepatic metastasis, and/or refractoriness to chemotherapy or radiation therapy (2-4). Therefore, the treatment of advanced ICC is shifting toward multidisciplinary approaches to improve patients' prognosis; however, surgical resection is currently considered the only curative treatment for ICC.

Predicting a patient's prognosis preoperatively on the basis of reliable biomarkers is very important in facilitating selection of the most appropriate treatment and postoperative follow-up strategies. Some studies have demonstrated that carbohydrate antigen 19-9 (CA19-9) is one of the most reliable postoperative prognostic markers (5). It has also been demonstrated that cancer-related inflammation is associated with tumor cell survival, proliferation, and metastasis (6, 7). Thus, biomarkers of cancer-related inflammation, such as preoperative neutrophil–to–lymphocyte ratio (NLR), platelet–to–lymphocyte ratio (PLR), and modified Glasgow prognostic score (mGPS) are established strong prognostic factors after curative resections of various cancers, including ICC (8-10). The mGPS is based on serum C-reactive protein (CRP) and albumin concentrations. It was recently reported that the CRP–to–albumin (CRP/Alb) ratio is associated with poor prognosis in patients with emergency medical admissions and sepsis (11, 12). In addition, the CRP/Alb ratio is reportedly a more important prognostic factor than mGPS in patients with HCC (13).

Hepatic resection is the only curative treatment for ICC; however, this modality is invasive and has a high treatment-related mortality and morbidity (14). Postoperative complications were recently reported to be related with recurrence-free survival (15). Thus, postoperative management is very important not only for postoperative quality of life, but also for prognosis. Various types of scores for predicting

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Key Words: Perioperative C-reactive protein/albumin ratio, intrahepatic cholangiocarcinoma, prognosis.

Table I. *Perioperative CRP/Alb ratios and patient prognosis.*

Timing of measurement	Postoperative prognosis (*p*-Value)
Preoperative (>0.024)	0.420
POD 1 (>0.737)	0.122
POD 3 (>2.077)	0.543
POD 7 (>0.732)	0.054
POD 14 (>0.304)	0.008
POM 1 (>0.094)	0.069
POM 3 (>0.034)	0.071

POD: Postoperative day; POM: postoperative month.

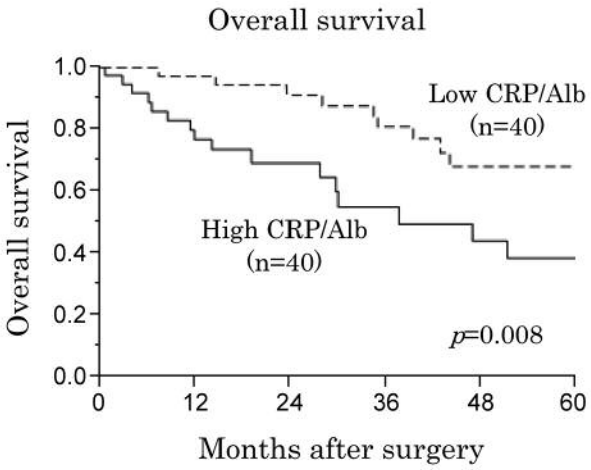

Figure 1. *Overall survival rates of patients with ICC who have undergone curative resection, according to CRP/Alb ratio on POD14. The high CRP/Alb group had a significantly poorer prognosis (p=0.008).*

whether patients can withstand surgery have been reported; however, the scores cannot predict patients' responses to undergoing radical surgery. In fact, clinical data sometimes change unexpectedly, especially when patients have undergone considerable surgical stress (16). Nevertheless, the relationship between prognostic scores based on postoperative inflammation and outcomes has not been established for ICC. Thus, we aimed to assess whether the perioperative CRP/Alb ratio influences the outcomes of patients with ICC after curative surgical resection.

Patients and Methods

Patients. Between April 2002 and December 2017, 100 patients with ICC underwent hepatic resection at our Institution. Of these 100 patients, 14 who had undergone repeated resection for ICC recurrence and six who had undergone non-curative resection were excluded; thus the final study cohort comprised 80 patients. As previously reported, surgical procedures were selected according to the size, number and site of the ICC and the patient's general and medical condition (17). CRP/Alb ratio was measured preoperatively (1–5 days before surgical resection), on postoperative days (POD) 1, 3, 7, 14, and on postoperative months (POM) 1 and 3. Our institution's Ethics Committee approved this study (#1291), and informed consent was obtained from all patients in accordance with Institutional Review Board protocols.

Surgical procedures. The details of our surgical indication and technique have been reported previously (17, 18). We do not routinely perform lymph node (LN) dissection, only when patients are suspected of having LN metastases on the basis of preoperative computed tomography scan, positron emission tomography, or macroscopic findings during the procedure (19, 20). For example, we suspect LN metastasis if LNs are 10 mm or larger on preoperative imaging or a hard texture is noted during the procedure. In such cases, we mainly perform LN dissection at #8 and #12 (19). Postoperative complications are defined as Grade III or greater according to the Clavien–Dindo classification (CD) (21).

Follow-up strategies. Clinical data, such as patient background characteristics, operative results, and pathological factors, were retrospectively obtained by the medical records of the 80 study patients. All patients involved were monitored either until March 2018 or their deaths. The mean follow-up period was 37 months. The ICCs were staged in accordance with the seventh edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging manual (22). Patients were followed up at our own hospital or at affiliated hospitals; tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), and CT or MRI were assessed every 3 or 4 months (18).

Statistical analysis. Continuous values were expressed as median (range). Continuous and categorical variables were compared using χ^2 tests or Student's *t*-tests, respectively. Survival analyses were performed using the Kaplan–Meier method, with comparisons by means of the log-rank test. Independent prognostic factors for poor OS were identified by multivariate Cox proportional hazard analysis and the clinicopathological factors associated with high CRP/Alb ratio were identified by stepwise logistic analysis. All cutoff points for CRP/Alb ratio are median values. The cut-off points for blood loss and operative time are also median values. All results with two-tailed values of $p<0.05$ were considered to be statistically significant. All statistical analyses were performed using JMP software (Version 12; SAS Institute, Cary, NC, USA).

Results

Relationship between perioperative CRP/Alb ratios and prognosis. To identify which perioperative CRP/Alb ratio most accurately predicts patients' prognosis, CRP/Alb ratios were measured preoperatively, on POD1, POD3, POD7, POD14, POM1, and POM3. Patients were divided into high and low CRP/Alb groups according to the median value and the data subjected to Cox proportional hazard analysis for OS. The median CRP/Alb ratios were 0.024, 0.74, 2.08, 0.73, 0.30, 0.09, and 0.03 preoperatively and on POD1, POD3, POD7, POD14, POM1, and POM3, respectively. The

Table II. *Patient characteristics according to CRP/Alb ratio on POD 14.*

Variables	CRP/Alb at POD 14		*p*-Value
	Low (≤0.30) n=40	High (>0.30) n=40	
Age (years)	65.5 (38-85)	71 (37-96)	0.0829
Gender (male/female)	18/22	31/9	0.0025
HBs-Ag(positive/negative)	6/34	2/38	0.1281
HCV-Ab(positive/negative)	8/32	6/34	0.5556
Liver damage (A/B)	39/1	39/1	0.9855
ICG R15 (%)	7.8 (0.8-27.6)	11.2 (1.9-27.3)	0.1460
CEA (ng/ml)	2.3 (0.7-36.8)	2.25 (0.7-2102)	0.4355
CA19-9 (U/l)	20.65 (0.2-8223)	26.85 (0.1-53373)	0.9539
Total bilirubin (mg/dl)	0.8 (0.1-1.7)	0.7 (0.3-1.6)	0.1122
Albumin (g/dl)	4.2 (3.4-5.1)	3.9 (2.7-4.8)	0.0182
PT (%)	100 (1.3-143)	100 (21-131)	0.6613
AST (U/l)	29 (12-163)	30 (7-134)	0.7722
ALT (U/l)	25 (5-285)	23 (7-188)	0.4708
CRP	0.06 (0.01-0.99)	0.16 (0.01-2.1)	0.0017

ALT: Alanine transaminase; AST: aspartate transaminase; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CRP: C-reactive protein; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; PT: prothrombin time.

Table III. *Operative and tumor-related factors according to CRP/Alb ratio on POD14.*

Variables	CRP/Alb at POD 14		*p*-Value
	Low (≤0.30) n=40	High (>0.30) n=40	
Operative factors			
Resection type (minor/major)	13/27	6/34	0.0813
Blood loss (ml)	425 (5-1974)	635 (29-2605)	0.0084
Operative time (min)	410 (221-610)	452 (259-799)	0.0433
Biliary resection (yes/no)	0/40	9/31	0.0011
Complication ≥CD IIIa (yes/no)	5/35	14/26	0.0163
Tumor-related factors			
Tumor size (mm)	32 (10-120)	35 (2-90)	0.4677
Tumor number (single/multiple)	34/6	34/6	1.0000
Vascular invasion (yes/no)	20/20	18/20	0.6542
pN stage (X/0/1)	15/11/4	16/11 /2	0.707
pStage (I/II/III/IV)	2/6/12/9	0/13/11/5	0.140

CD: Clavien-Dindo.

p-values on Cox-proportional hazard analysis were 0.420, 0.122, 0.543, 0.054, 0.008, 0.069, and 0.543 preoperatively and on POD1, POD3, POD7, POD14, POM1, and POM3, respectively (Table I). The only statistically significant association was between POD14 and OS. OS curves according to high and low CRP/Alb are shown in Figure 1.

Clinicopathological factors associated with high CRP/Alb ratio on POD 14. Next, we compared selected clinicopathological factors between the high and low CRP/Alb groups on POD14 (Table II). A high CRP/Alb ratio on POD14 was significantly associated with the clinical characteristics of male sex (p=0.0025), low serum albumin (p=0.0182), and high CRP (p=0.0017). No tumor-related factors were significantly associated with OS (Table III). As to operative factors, a high CRP/Alb ratio on POD14 was significantly associated with longer operation time (p=0.0433), more intraoperative bleeding (p=0.0084), higher morbidity rate (p=0.0163), and higher rate of biliary resection (p=0.0011) (Table III). To determine which clinicopathological factors

Table IV. *Relationships between clinicopathological factors and CRP/Alb ratio on POD 14.*

Factors	Univariate analysis		Multivariate analysis		
	Odds ratio	*p*-Value	Odds ratio	95%CI	*p*-Value
Age ≥65	2.71	0.035	4.34	1.46-14.63	0.0076
Gender (male)	4.21	0.003	5.89	2.03-19.43	0.0008
HBs-Ag (positive)	3.35	0.128			ns
HCV-Ab (positive)	1.42	0.556			ns
ICG R15 ≥10%	2.02	0.143			ns
CEA ≥3.4	2.40	0.082			ns
CA19-9 ≥37	1.10	0.822			ns
Blood loss ≥525 ml	2.81	0.024			ns
Operative time ≥445 min	2.50	0.043			ns
Multiple tumors ≥2	1.00	1.00			ns
Tumor size ≥50 mm	1.44	0.458			ns
pN (+)	1.07	0.929			ns
Vascular invasion (+)	1.22	0.654			ns
Complication(+) ≥CD IIIa	3.77	0.016	8.45	2.14-43.44	0.0016

CA19-9: Carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody.

Table V. *Prognostic factors for OS.*

Factors	Univariate		Multivariate analysis		
	HR	*p*-Value	HR	95%CI	*p*-Value
Age ≥65	1.25	0.549			ns
Gender (male)	0.84	0.640			ns
HBs-Ag (positive)	0.57	0.320			ns
HCV-Ab (positive)	1.35	0.559			ns
ICG R15 ≥10%	1.82	0.112			ns
CEA ≥3.4	1.45	0.391			ns
CA19-9 ≥37	1.34	0.420			ns
Blood loss ≥525 ml	1.34	0.425			ns
Operative time ≥445 min	1.33	0.425			ns
Multiple tumors ≥2	1.22	0.675			ns
Tumor size ≥50 mm	0.95	0.901			ns
pN (+)	3.71	0.008	4.53	1.71-10.68	0.004
Vascular invasion (+)	1.44	0.313	2.91	1.16-6.03	0.020
Complication(+) ≥CD IIIa	2.86	0.010	2.91	1.28-6.38	0.012
CRP/Alb POD 14 >0.28	2.58	0.001	2.62	1.21-5.88	0.014

CA19-9: Carbohydrate antigen; CEA: carcinoembryonic antigen; 19-9HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody.

were independently associated with the CRP/Alb ratio at POD14, selected clinicopathological factors were divided into two groups according to their median values and subjected to logistic regression analysis (Table IV). In this multivariate analysis, age (≥65) [odds ratio (OR)=4.34, p=0.0076], male sex (OR=5.89, p=0.0008), and the presence of complications (OR=8.45, p=0.0016) were independently associated with CRP/Alb ratio on POD14. Finally, to assess whether CRP/Alb ratio on POD14 more accurately predicts ICC outcomes than other clinicopathological factors, Cox proportional hazard analysis for OS was performed (Table V). Pathological lymph node metastasis (p=0.004), pathological vascular invasion (p=0.020), presence of complications (p=0.012) and high CRP/Alb ratio at POD 14 (p=0.014) were thus identified as independent prognostic factors for poor OS.

Discussion

To the best of our knowledge, this is the first study to implicate postoperative and perioperative inflammatory score

and nutrition scores in the prognosis of patients with ICC who have undergone curative resections. Although surgery is the most effective medical treatment for solid tumors, surgical resection is invasive. In particular, resection of ICC sometimes requires major hepatectomy and can result in serious complications such as liver failure or bile leakage (14). Furthermore, comorbidities, such as hypertension and diabetes mellitus are becoming common in older patients undergoing invasive surgery. Although the safety of modern surgical procedures has improved, the risks of morbidity and mortality remain high in these patients. In past reports, the risk of postoperative complications has been estimated by the Physiological and Operative Severity Score for the Enumeration Mortality and Morbidity (POSSUM) and the Estimation of Physiology Ability and Surgical Stress (E-PASS) scoring system, both of which are based on preoperative factors (23, 24). On the other hand, biological reactions by surgical stress differ between patients. Experienced gastroenterological surgeons know that patients with perioperative high inflammation and perioperative low nutritional markers are likely to have poor postoperative outcomes, these being indicators of a patient's probable response to surgical stress.

In this study, we assessed the relationship between perioperative CRP/Alb ratio and clinical outcomes of patients with ICC. Of the CRP/Alb ratios at different perioperative points, the ratio on POD 14 was significantly associated with prognosis. We believe that one of the main reasons for this finding is that postoperative complications are associated with an increase in serum CRP and a decrease in serum Alb concentration. In fact, the presence of complications was found to be independently associated with a high CRP/Alb ratio on POD14 (Table III). The prognostic value of the CRP/Alb ratio on POD14 has also been demonstrated in patients with pancreatic ductal adenocarcinoma; specifically, a high ratio was significantly associated with poor OS and relapse-free survival (25). In the present study, the CRP/Alb on POD14 was also associated with the volume of intraoperative blood loss and the duration of the surgical procedure, as well as with older age, which is subsequently linked with severe surgical stress. According to Watt *et al*. (16), the mGPS on POD 3 is associated with OS and major infectious complications in patients with colorectal cancer who underwent curative resection. However, they investigated the mGPS at only two points, namely on POD 3 and POD 4.

So what is the clinical usefulness of the CRP/Alb ratio on POD 14? We believe that it would assist the postoperative management. For example, patients with high CRP/Alb ratios on POD14 may be good candidates for adjuvant chemotherapy. So far, there is no evidence for the clinical effectiveness of adjuvant chemotherapy after resection of bile duct cancer. Ebata *et al*. have reported that the probability of survival after resection of bile duct cancer did not differ significantly between patients who received gemcitabine adjuvant chemotherapy and those who were simply observed (26).

The current study had several limitations. First, it was retrospective study and included relatively few patients with ICC attending a single institution. Second, several factors that can affect perioperative inflammation-based and nutritional scores such as medications and meals varied between patients. Thus, a large-scale prospective study is required to confirm our findings.

In conclusion, the CRP/Alb ratio on POD14 is an independent prognostic factor in patients with ICC who have undergone curative resections.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

YN and YY participated in the conception, design, analysis of this study and drafted the manuscript. KA, TM, RI, TY, NU, TY, SN, HO and KI participated in the statistical analysis and revised it. TA and HB conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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