Pre-treatment C-Reactive Protein as a Prognostic Factor for Recurrence after Surgical Resection of Hepatocellular Carcinoma

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Abstract. *Background and Aims: We examined the prognostic value of pre-treatment C-reactive protein (CRP) after surgical resection (SR) for hepatocellular carcinoma (HCC). Patients and Methods: A total of 298 patients with HCC who underwent SR were analyzed. They were categorized into a CRP-positive group (group A: CRP >0.2 mg/dl, n=130) and a CRP-negative group (group B: CRP <0.2 mg/dl, n=168). Overall survival (OS) and recurrence-free survival (RFS) were compared. Results: The 1- and 3-year cumulative OS rates were 87.0% and 68.3% in group A and 95.9% and 81.1% in group B (p=0.194). The corresponding RFS rates were 61.6% and 30.3% in group A and 77.2% and 44.9% in group B (p=0.004). In multivariate analysis, the pre-treatment CRP level was a significant prognostic factor linked to RFS (p=0.046). Conclusion: Pre-treatment CRP levels may be a useful predictor of recurrence after SR for HCC.*

Hepatocellular carcinoma (HCC) is a major health problem worldwide, with an estimated incidence of 500,000 million new cases annually. It is the fifth most common type of cancer in the world, and the third most common cause of cancer-related death (1, 2). The prognosis of HCC is generally poor because of its high recurrence rate (1, 3, 4). Surgical resection (SR) remains the best curative treatment, but is only suitable in 9-27% of patients. The presence of significant background liver cirrhosis often precludes hepatic resection in patients with HCC. Recurrence in the remnant liver is also common in patients who have undergone radical hepatic resection (5).

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Several investigators have reported on the degree of liver damage, maximum tumor diameter, number of tumors, blood loss during surgery, microscopic vascular invasion (MVI), surgical curability, and free surgical margins as prognostic factors in patients with HCC who underwent SR (6-12). However, most of these factors are based on the postoperative status and pathological results. In addition to tumor characteristics and liver function, other easy-to-perform and widely-available prognostic markers are required to more accurately predict clinical outcomes after SR.

C-Reactive protein (CRP) is an acute-phase reactant synthesized by hepatocytes as part of the inflammatory response, and regulated by pro-inflammatory cytokines such as interleukin (IL)-6 and IL-1β (13-16). Determination of serum CRP is generally inexpensive, widely-available and routinely performed in clinical practice. Serum CRP levels have also been reported to be a prognostic factor in various malignancies, including breast, colorectal, gastric, esophageal, and urological cancer, and in multiple myeloma (17-22). However, to the best of our knowledge, there have been few reports regarding the relationship between pre-treatment CRP levels and survival in patients with HCC undergoing SR (23-25). The present study therefore aimed to examine the prognostic value of pre-treatment CRP levels after SR for HCC.

Patients and Methods

Patients. Patients were selected for SR based on assessments of tumor characteristics, remnant liver volume and general condition, through discussion with experienced surgeons, radiologists and physicians. SR was performed in 342 treatment-naïve patients with HCC at the Department of Surgery, Osaka Red Cross Hospital, Japan, between January 2004 and June 2012. Out of these, we excluded patients operated on without curative intent (n=41) and with surgery-related death (n=3). Curative surgery was defined as the resection of all tumors detectable using imaging modalities. A total of 298 patients with HCC who underwent SR were therefore analyzed in the present study.

Serum CRP levels were measured using a C-reactive protein kit (Nanopia® CRP, Sekisui Medical Co., Ltd, Tokyo, Japan). Serum CRP levels <0.2 mg/dl were defined as normal in our hospital, and

we therefore classified the analyzed patients into two groups: a CRP-positive group (group A: serum CRP level ≥0.2 mg/dl, n=130) and a CRP-negative group (group B: serum CRP level <0.2 mg/dl, n=168). The serum CRP level in group A ranged from 0.2-16.9 mg/dl (median=0.3 mg/dl).

Routine laboratory measurements were performed on the day of admission to exclude any inflammatory effects of pre-operative invasive procedures such as transcatheter arterial chemoembolization (TACE). At this time, no clinical evidence of infection or any other inflammatory conditions were found in any patient.

Written informed consent was obtained from all patients prior to surgery, and the study protocol complied with all of the provisions of the Declaration of Helsinki. The ethics committee of our hospital approved the protocol for our study. The present study comprised of a retrospective analysis of patient records, and all treatments were conducted in an open-label manner.

HCC diagnosis. HCC was diagnosed using abdominal ultrasound and dynamic computed tomography (CT) scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase) and/or magnetic resonance imaging (MRI), based mainly on the recommendations of the American Association for the Study of Liver Diseases (26). Arterial and portal-phase dynamic CT images were obtained at approximately 30 s and 120 s, respectively, after the injection of the contrast material. Abdominal angiography combined with CT assistance was performed in all patients before SR, in line with the recommendations of Yamasaki *et al*., who reported the usefulness of this technique for detecting small satellite nodules (27). HCC stage was determined using the Liver Cancer Study Group of Japan staging system (28). HCC was confirmed pathologically in resected specimens at surgery, except for cases with complete necrosis.

Hepatectomy and surgical procedure. All procedures were performed by one of four surgeons with at least 10 years experience of SR.

Anatomical SR was defined as a resection in which tumors are completely removed anatomically on the basis of Couinaud's classification (segmentectomy, sectionectomy, and hemihepatectomy or extended hemihepatectomy). Non-anatomical partial SR was carried out as a limited resection or tumor enucleation. Anatomical SR was performed in 134 patients (45.0%) and non-anatomical SR was performed in 164 patients (55.0%) in the present study. Conventional open hepatectomy was performed in 230 patients (77.2%) and laparoscopic hepatectomy was performed in 68 patients (22.8%) in the current study. Conventional open hepatectomy was carried out under general anesthesia using a right subcostal incision with a midline extension. We performed anatomic partial hepatectomy with a resection margin of at least 1 cm over the tumor, based on intraoperative ultrasonography (IOUS) guidance. IOUS was performed routinely to estimate the location, size, number and feeding vessels of the tumor, as well as to provide a clear vascular map of the liver anatomy. The Cavitron Ultrasonic Aspiration system (CUSA, Valley Lab Corp., New York, USA) was used to dissect the liver tissue. Hemostasis was achieved by dipolar electric coagulation and suturing. The Pringle maneuver was usually used in cases with cirrhotic liver, with a clamp/unclamp time of 15 min/5 min policy. Laparoscopic hepatectomy was performed using the four-trocar technique. The first trocar was placed via a small incision below the umbilicus for pneumoperitoneum creation. The tumor extent and its relationship with the vascular anatomy and other tumors in the liver were explored using IOUS. The line of the intended liver parenchymal transection was marked on the surface of the liver using diathermy. Ultrasonic dissection was performed using an ultrasonic surgical system. The resected liver was maneuvered into a plastic bag (29).

TACE was performed prior to surgery in 110 patients, transcatheter arterial infusion chemotherapy in 53 patients, and transcatheter arterial embolization in 10 patients. These procedures were conducted based mainly on the decisions of the attending physicians. Patients were discharged when their liver function returned to normal and any adverse events had resolved after SR.

Follow-up. Follow-up after surgery consisted of periodic blood tests and monitoring of tumor markers, including α-fetoprotein (AFP) and *des*-γ-carboxy prothrombin (DCP), using a chemiluminescent enzyme immunoassay (Lumipulse PIVKAII Eisai; Eisai, Tokyo, Japan). Dynamic CT scans and/or MRI were obtained every 3-4 months after SR. Chest CT, whole abdominal CT, brain MRI, and bone scintigraphy were performed when extrahepatic HCC recurrences were suspected.

Statistical analysis. Data were analyzed using univariate and multivariate analyses. Continuous variables were compared using unpaired *t*-tests, and categorical variables were compared using Fisher's exact tests. Time to recurrence was defined as the interval between surgery and first confirmed recurrence. For analysis of recurrence-free survival (RFS), follow-up ended at the time of first recurrence; other patients were censored at their last follow-up visit or the time of death from any cause without recurrence. For analysis of overall survival (OS), follow-up ended at the time of death from any cause, and the remaining patients were censored at the last follow-up visit. The cumulative OS and RFS rates were calculated using the Kaplan–Meier method, and tested using the log-rank test. The Cox proportional hazards model was used for multivariate analysis of factors that were considered significant in univariate analysis. These statistical methods were used to estimate the interval from surgery. Data were analyzed using SPSS software, version 11.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Data are expressed as means±standard deviation (SD). Values of $p<0.05$ were considered to be statistically significant.

Results

Baseline characteristics. The baseline characteristics of patients in group A (n=130) and B (n=168) are shown in Table 1. The mean ages of patients in group A and group B did not differ significantly ($p=0.693$). The mean observation periods were 2.9±2.1 years in group A and 3.0±2.0 years in group B, respectively. In terms of HCC stage, significant difference was observed in the two groups ($p<0.001$). Group A had significantly more HCC patients with multiple tumors compared with group B ($p=0.002$), and the maximum tumor size was 5.8±3.3 cm in group A compared with 3.9±2.1 cm in group B ($p<0.001$), indicating that patients in group A had more advanced tumor characteristics than those of group B.

Cumulative OS and RFS rates. The 1-, 3- and 5-year cumulative OS rates were 87.0%, 68.3% and 59.7%, respectively, in group A and 95.9%, 81.1% and 60.6%, respectively, in group B ($p=0.194$) (Figure 1). The

Table I. *Baseline characteristics between the C-Reactive protein (CRP)-positive group (group A) and the CRP-negative group (group B).*

	Group A (n=130)	Group B (n=168)	*p*-Value
Gender (male/female)	100/30	122/46	0.424[a]
Age (years)	67.7±10.5	68.1±10.1	0.693[b]
Hepatectomy			
Anatomical/non-anatomical	71/59	63/105	0.003[a]
HCC stage (I/II/III/IV)	5/63/42/20	14/112/39/3	<0.001[a]
Etiology (HBV/HCV/nBnC)	17/57/56	23/120/25	<0.001[a]
Child-Pugh classification (A/B)	126/4	162/6	>0.999[a]
Tumor number (single/multiple)	72/58	122/46	0.002[a]
Maximum tumor size (cm)	5.8±3.3	3.9±2.1	<0.001[b]
AST (IU/l)	57.7±50.8	57.0±38.2	0.885[b]
ALT (IU/l)	49.6±49.0	54.7±42.2	0.329[b]
Serum albumin (g/dl)	3.82±0.50	4.01±0.50	0.001[b]
Total bilirubin (mg/dl)	0.83±0.45	0.83±0.42	0.918[b]
Prothrombin time (%)	88.9±14.0	89.8±14.8	0.610[b]
Platelets ($\times 10^4/mm^3$)	16.5±7.6	13.2±6.6	<0.001[b]
ICGR 15 (%)	14.2±10.1	14.1±10.2	0.962[b]
AFP (ng/ml)	3961.8±18558.0	1370.8±4716.8	0.124[b]
DCP (mAU/ml)	10214.9±48152.6	2811.8±10627.9	0.089[b]
HCC histology			
Well/moderate/poorly/necrosis	10/68/47/5	13/84/54/17	0.230[a]
Fibrous capsule (yes/no)	98/32	134/34	0.400[a]
Capsular invasion (yes/no)	75/55	93/75	0.725[a]
Microscopic vascular invasion (yes/no)	64/66	54/114	0.003[a]
Microscopic surgical margin (yes/no)	40/90	48/120	0.702[a]

CRP: C-Reactive protein; HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICGR 15: indocyanine green retention at 15 min; AFP: alpha-fetoprotein; DCP: des-γ-carboxy prothrombin; [a]Fisher,s exact test; [b]unpaired *t*-test.

corresponding RFS rates in the two groups were 61.6%, 30.3% and 20.1%, and 77.2%, 44.9% and 21.2%, respectively, (p=0.004) (Figure 2).

Univariate analysis of factors contributing to OS and RFS. Univariate analysis identified the following factors as being significantly associated with OS: HCC stage (p<0.001); maximum tumor size (p=0.030); tumor number (p<0.001); serum albumin ≥4.0 g/dl (p=0.008); total bilirubin ≥1 mg/dl (p=0.045); AFP ≥100 ng/ml (p<0.001); *des*-γ-carboxy prothrombin (DCP) ≥100 mAU/ml (p=0.005); and microscopic vascular invasion (MVI) (p<0.001) (Table II). Significant factors associated with RFS were: HCC stage (p<0.001); maximum tumor size (p=0.005); tumor number (p<0.001); pre-treatment CRP levels (p=0.004); aspartate aminotransferase (AST) ≥50 IU/l (p=0.007); alanine aminotransferase (ALT) ≥50 IU/l (p=0.005); AFP ≥100 ng/ml; (p=0.012) and MVI (p<0.001) (Table II).

Multivariate analysis of factors contributing to OS and RFS. The hazard ratios (HRs) and 95% confidence intervals (CIs) calculated using multivariate analysis for the eight factors found to be significantly associated with OS using univariate analysis are detailed in Table III. Total bilirubin ≥1 mg/dl (p=0.003), serum albumin ≥4.0 g/dl (p=0.005), AFP >100 ng/ml (p<0.001) and MVI (p<0.001) were found to be significant independent factors linked to OS. The HRs and 95% CIs calculated using multivariate analysis for the eight factors significantly associated with RFS in univariate analysis are detailed in Table IV. Tumor number (p=0.015), serum CRP level (p=0.046) and MVI (p=0.015) were found to be significant independent factors associated with RFS.

Causes of death. Forty patients in group A (30.8%) died during the follow-up period. The causes of death were HCC recurrence in 32 patients, liver failure in four patients and miscallaneous causes in four. Forty-two patients in group B (25.0%) died during the follow-up period, and the causes of death were HCC recurrence in 27 patients, liver failure in 10 and miscellaneous causes in five.

HCC recurrence. In the present study, 89 (68.5%) patients in group A and 83 (49.4%) patients in group B had HCC recurrence during the follow-up period. The patterns of HCC recurrence after SR in group A were: single HCC recurrence in the liver in 33 patients; multiple HCC recurrences in the liver in 43 patients; multiple HCC recurrences in the liver with lung metastases in five patients; multiple HCC recurrences in

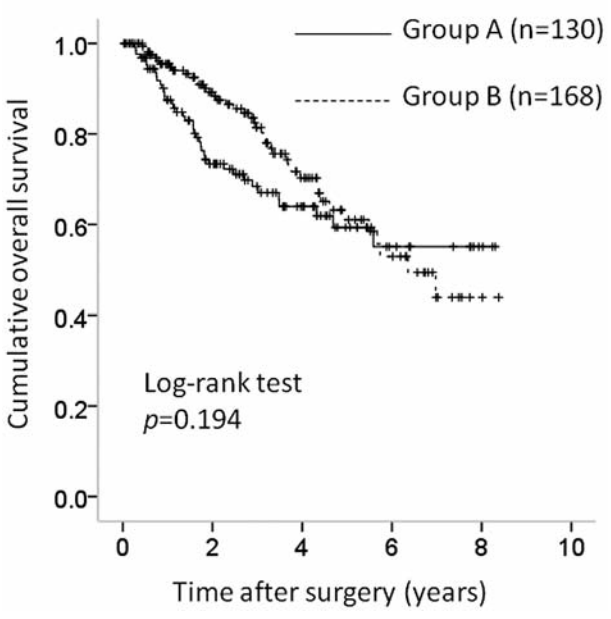

Figure 1. *Cumulative overall survival (OS) rates in the C-Reactive protein (CRP)-positive (group A, n=130) and CRP-negative (group B, n=168) groups. The 1-, 3- and 5-year cumulative OS rates in the two groups were 87.0%, 68.3% and 59.7%, respectively, in group A, and 95.9%, 81.1% and 60.6%, respectively, in group B (p=0.194).*

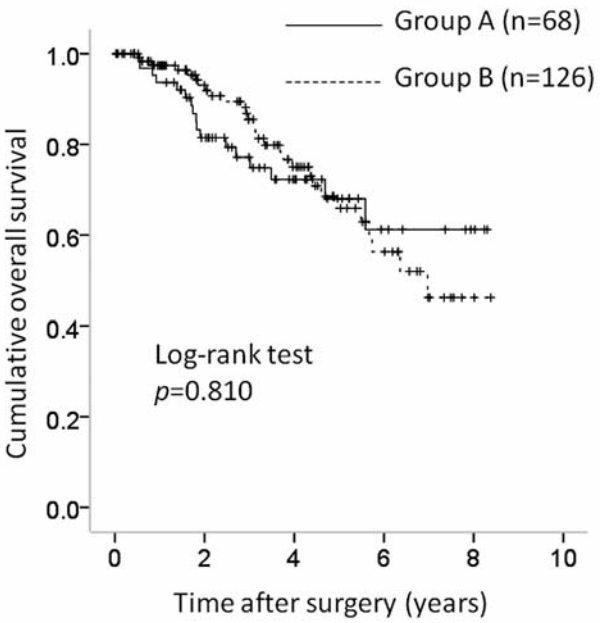

Figure 2. *Cumulative recurrence-free survival (RFS) rates in the C-Reactive protein (CRP)-positive (group A, n=130) and CRP-negative (group B, n=168) groups. The 1-, 3- and 5-year cumulative RFS rates in the two groups were 61.6%, 30.3% and 20.1%, respectively, in group A, and 77.2%, 44.9% and 21.2%, respectively, in group B (p=0.004).*

Table II. *Univariate analysis contributing to overall survival (OS) and recurrence-free survival (RFS) for all cases (n=298).*

Variables	n	OS *p*-Value[a]	RFS *p*-Value[a]
Age >70 years (yes/no)	153/145	0.253	0.658
Gender (male/female)	222/76	0.619	0.201
Cause of liver disease			
Hepatitis B/hepatitis C/non-B non-C	40/177/81	0.268	0.771
HCC stage (I, II/III, IV)	194/104	<0.001	<0.001
Maximum tumor size ≥5 cm (yes/no)	104/194	0.030	0.005
Tumor number (single/multiple)	194/104	<0.001	<0.001
Serum CRP (positive/negative)	130/168	0.194	0.004
ICGR15 ≥14% (yes/no)	123/175	0.078	0.154
Total bilirubin ≥1.0 mg/dl (yes/no)	78/220	0.045	0.143
Serum albumin ≥4.0 g/dl (yes/no)	150/148	0.008	0.446
AST ≥50 IU/l (yes/no)	132/166	0.124	0.007
ALT ≥50 IU/l (yes/no)	115/183	0.057	0.005
Platelets $\geq 15\times10^4/mm^3$ (yes/no)	127/171	0.693	0.717
Prothrombin time ≥80% (yes/no)	218/80	0.381	0.117
AFP ≥100 ng/ml (yes/no)	91/207	<0.001	0.012
DCP ≥100 mAU/ml (yes/no)	190/108	0.005	0.057
Microscopic capsule (yes/no)	232/66	0.817	0.427
Microscopic capsule invasion (yes/no)	168/130	0.155	0.339
Microscopic vascular invasion (yes/no)	118/180	<0.001	<0.001
Microscopic surgical margin (yes/no)	88/210	0.275	0.991

HCC: Hepatocellular carcinoma; CRP: C-Reactive protein; ICGR 15: indocyanine green retention at 15 min; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; DCP: des-γ-carboxy prothrombin; [a]Log-rank test.

Table III. *Multivariate analysis contributing to overall survival after surgical resection.*

Variable	Hazard ratio	95% Confidence interval	*p*-Value[a]
HCC stage			
I or II	1.188	0.470-3.012	0.717
III or IV	1.000		
Maximum tumor size			
≥5 cm	0.899	0.534-1.515	0.690
<5 cm	1.000		
Tumor number			
Single	1.000		
Multiple	0.563	0.231-1.372	0.206
Total bilirubin			
≥1.0 mg/dl	0.471	0.285-0.778	0.003
<1.0 mg/dl	1.000		
Serum albumin			
≥4.0 g/dl	1.983	1.228-3.202	0.005
<4.0 g/dl	1.000		
AFP			
≥100 ng/ml	0.436	0.277-0.686	<0.001
<100 ng/ml	1.000		
DCP			
>100 mAU/ml	0.600	0.341-1.056	0.076
<100 mAU/ml	1.000		
Microscopic vascular invasion			
Yes	0.369	0.224-0.608	<0.001
No	1.000		

HCC: Hepatocellular carcinoma; AFP: alpha-fetoprotein; DCP: des-γ-carboxy prothrombin; [a]Cox proportional hazard model.

Table IV. *Multivariate analysis contributing to recurrence-free survival after surgical resection.*

Variable	Hazard ratio	95% Confidence interval	*p*-Value[a]
HCC stage			
I or II	1.006	0.507-1.996	0.129
III or IV	1.000		
Maximum tumor size			
≥5 cm	0.930	0.655-1.321	0.687
<5 cm	1.000		
Tumor number			
Single	1.000		
Multiple	0.426	0.215-0.845	0.015
Serum CRP			
Positive	0.740	0.535-0.924	0.046
Negative	1.000		
AST			
≥50 IU/l	0.906	0.581-1.413	0.664
<50 IU/l	1.000		
ALT			
≥50 IU/l	0.764	0.485-1.203	0.245
<50 IU/l	1.000		
AFP			
≥100 ng/ml	0.736	0.533-1.017	0.063
<100 ng/ml	1.000		
Microscopic vascular invasion			
Yes	0.654	0.467-0.916	0.015
No	1.000		

HCC: Hepatocellular carcinoma; CRP: C-Reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; [a]Cox proportional hazard model.

the liver with lymph node metastasis in four patients; multiple HCC recurrences in the liver with peritoneal dissemination in three patients; and single brain metastasis in one patient. The patterns of HCC recurrence after SR in group B were: single HCC recurrence in the liver in 31 patients; single HCC recurrence with invasion of the main portal vein in one patient; multiple HCC recurrences in the liver in 47 patients; multiple HCC recurrences in the liver with lung metastases in three patients; and single lymph node metastasis in one patient.

Treatment methods for the first recurrence in group A were: SR in four patients; radiofrequency ablation (RFA) in 40 patients; TACE in 22 patients; percutaneous ethanol injection (PEI) in four patients; systemic chemotherapy in seven patients and no specific treatment in 12 patients. The treatment methods used in group B were: SR in eight patients; RFA in 42 patients; TACE in 23 patients; PEI in four patients; systemic chemotherapy in three patients and no specific treatment in three patients.

Surgery-related serious adverse events (SAEs). Surgery-related SAEs in group A included abscess formation in five patients, bile leakage in five patients, refractory ascites in five patients, aspiration pneumonia in three patients, gastrointestinal bleeding in one patient, acute heart failure in one patient, and acute respiratory distress syndrome in one patient. Equivalent complications in group B included abscess formation in five patients, bile leakage in six patients, refractory ascites in nine patients, aspiration pneumonia in one patient, gastrointestinal bleeding in one patient, perforation of the small intestine in one patient, acute respiratory distress syndrome in one patient and brain infarction in one patient. All these SAEs improved during the same hospitalization. There was no significant difference between the two groups in terms of SAEs related to surgery (p=0.872).

Subgroup analysis in HCC patients with stage I and II HCC (n=194). Because group A patients had more advanced tumor characteristics than group B, we performed a subgroup analysis according to HCC stage. There were 68 patients with stage I and II HCC in group A and 126 patients with stage I and II HCC in group B. There was no significant difference between the two groups in patients with HCC stage I and II, in terms of either OS or RFS (p=0.810 and p=0.905) (Figures 3 and 4).

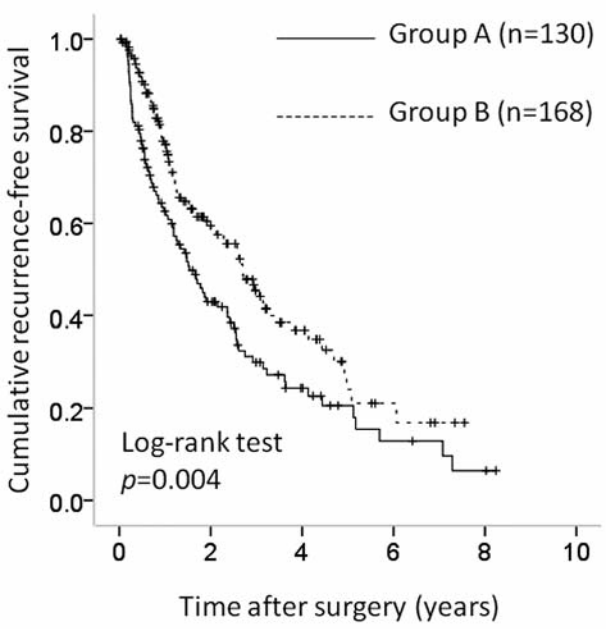

Figure 3. *Subgroup analysis in patients with stage I and II hepatocellular carcinoma (HCC) (n=194) in terms of overall survival (OS). There were 68 patients with stage I and II HCC in the CRP-positive group (group A) and 126 patients with stage I and II HCC in the CRP-negative group (group B). There was no significant difference between the two groups in terms of OS (p=0.810).*

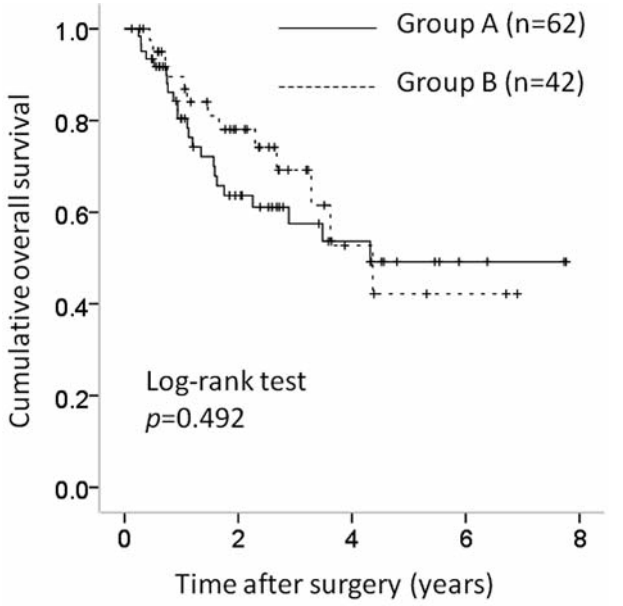

Figure 5. *Subgroup analysis in patients with stage III and IV hepatocellular carcinoma (HCC) (n=104) in terms of overall survival (OS). There were 62 patients with stage III and IV HCC in the C-Reactive protein (CRP)-positive group (group A) and 42 patients with stage III and IV HCC in the CRP-negative group (group B). There was no significant difference between the two groups in patients with stage III and IV HCC in terms of OS (p=0.492).*

Subgroup analysis in HCC patients with stage III and IV HCC (n=104). There were 62 patients with stage III and IV HCC in group A and 42 patients with stage III and IV HCC in group B. There was no significant difference between the two groups in patients with HCC stage III and IV in terms of OS (p=0.492) (Figure 5). However, RFS did significantly differ between the two groups (p=0.011) (Figure 6). Patients with stage III and IV HCC in group A had a significantly lower RFS rate than those in group B.

Discussion

Although many studies have investigated the prognostic factors after SR for resectable HCC, there have been few reports on the relationship between pre-treatment CRP levels and survival in patients with resectable HCC (23-25).

In the present study, pre-treatment CRP levels were significantly associated with RFS after SR in multivariate analysis for all cases (p=0.046), and there was a significant difference between CRP-positive and CRP-negative patients in terms of RFS in the subgroups with HCC stage III and IV HCC (p=0.011). However, pre-treatment CRP levels were not a significant prognostic factor in multivariate analysis in terms of OS. These results suggest that the pre-treatment CRP levels are a useful predictive factor for HCC recurrence after SR, and provide a rationale for the measurement of serum CRP levels in future clinical trials in patients with HCC.

In terms of tumor characteristics, group A had more advanced tumor characteristics than group B, and the proportion of HCC recurrence with extrahepatic metastasis in group A was significantly higher than in group B [13 (14.6%) out of 89 patients with HCC recurrence in group A *vs.* 4 (4.8%) out of 83 patients with HCC recurrence in group B, p=0.040]. These results suggest that high serum CRP levels may reflect tumor aggressiveness or the systemic dissemination of tumor cells (23).

In contrast, serum CRP levels were not a significant factor in terms of either OS or RFS in the subgroup of patients with stage I and II HCC, indicating that serum CRP was not a useful prognostic factor for survival in early-stage HCC after SR.

Inflammation promotes cancer cell proliferation and stimulates angiogenesis and metastasis. Inflammatory cytokines such as IL-6 and IL-1β, which are known to be major regulators of CRP production, are linked to transcriptional signaling pathways associated with carcinogenesis, cancer growth and cancer invasion in various malignancies. This relationship may provide a possible mechanism explaining the association between high CRP levels and poor clinical outcome in patients with HCC (15, 16).

Total bilirubin and serum albumin level reflect hepatic functional reserve and were significant prognostic factors

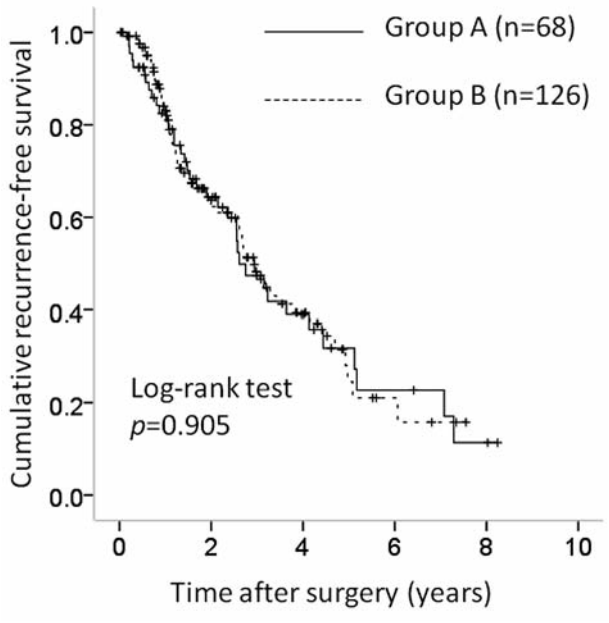

Figure 4. *Subgroup analysis in patients with stage I and II hepatocellular carcinoma (HCC) (n=194) in terms of recurrence-free survival (RFS). There was no significant difference between the two groups in terms of RFS (p=0.905).*

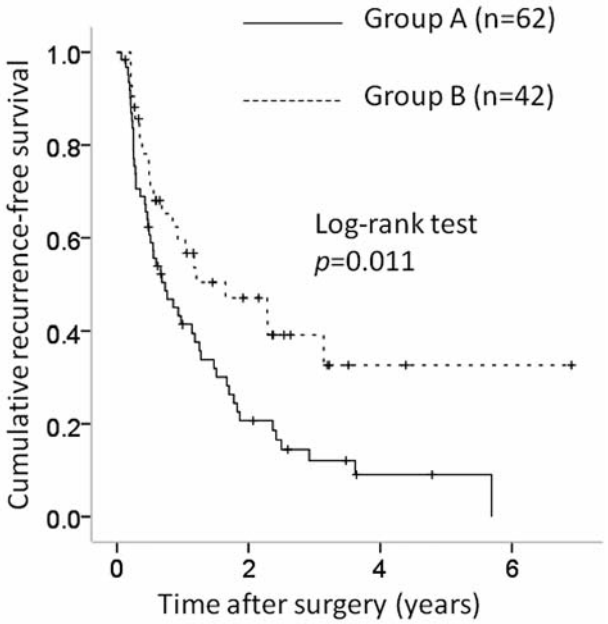

Figure 6. *Subgroup analysis in patients with stage III and IV hepatocellular carcinoma (HCC) (n=104) in terms of recurrence-free survival (RFS). There was a significant difference between the groups in patients with stage III and IV HCC in terms of RFS (p=0.011).*

linked to OS in multivariate analysis. Branched-chain amino acid therapy may, thus, be an effective treatment to optimize clinical outcomes in HCC patients with poor hepatic functional reserve (30).

Multivariate analysis identified MVI as a significant predictive factor linked to both OS and RFS. The predictive value of MVI for survival after SR for HCC may be explained by the fact that MVI caused by HCC tumor cells provides an important route for intrahepatic metastasis, and can, thus, lead to poorer survival. Lim *et al*. reported that MVI was a better predictor of tumor recurrence and OS than the Milan criteria after SR for HCC (10). Our results were in accordance with their report, suggesting that close observation after SR is needed in these patients.

The serum AFP levels were a significant factor in terms of OS, and marginally significant in terms of RFS in multivariate analysis. Gómez-Rodríguez *et al*. reported that serum AFP had prognostic value in patients with HCC, and that the addition of AFP could improve the Barcelona Clinic Liver Cancer System (31). Our results were consistent with their report.

There were no significant differences between groups A and B in terms of surgery-related SAEs, suggesting no effect of pre-treatment CRP levels on surgical morbidity.

There were several limitations to the current study. Firstly, this was a retrospective study. Secondly, the mean observation periods were relatively short for survival analysis. Thirdly, because most patients with HCC have liver dysfunction due to liver cirrhosis, and the liver is the only organ that produces CRP, serum CRP levels might be underestimated in patients with HCC with poor hepatic function. Fourthly, various conditions, such as infection, could also affect serum CRP levels. Further studies are therefore needed to verify the results of this study. However, the current results indicate that the pre-treatment serum CRP levels are closely-associated with HCC recurrence after SR, and suggest that it may be a useful prognostic factor for HCC recurrence after SR.

Conflicts of Interest

The Authors have not received any financial support for this study and have no conflicts of interest to declare.

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