

Clinical Science

Usefulness of a new inflammation-based scoring system for prognostication of patients with hepatocellular carcinoma after hepatectomy



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Tumor marker;
Inflammation

Abstract

BACKGROUND: We investigated whether a preoperative scoring system (the “CRP-AFP Score [CAS]”) based on the serum levels of C-reactive protein and alpha-fetoprotein would predict outcome in patients undergoing hepatectomy for hepatocellular carcinoma.

METHODS: The CAS was defined as follows: patients with an elevated level of both C-reactive protein (>.3 mg/dL) and alpha-fetoprotein (>20 ng/mL) were assigned a score of 2, and patients showing one or none of these abnormalities were assigned a score of 1 or 0, respectively.

RESULTS: A total of 349 patients were identified. Pathologic findings, in terms of tumor size, histologic grade, vascular invasion, intrahepatic metastasis, and recurrence rate, worsened as the CAS increased. CAS 2 patients had a poorer 5-year overall survival than CAS 0 or 1 patients (32.2% vs 59.7% vs 49.2%, respectively; $P < .001$).

CONCLUSIONS: The CAS is an informative scoring system that can predict outcome in patients with hepatocellular carcinoma after hepatectomy.

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Hepatocellular carcinoma (HCC) remains the most common cancer in Japan, mainly because of the high prevalence of hepatitis C virus (HCV) infection.¹ To reduce HCC-related mortality, various surgical modalities such as liver resection and liver transplantation have been established and these can offer the chance of potential cure, the 5-year overall survival (OS) currently standing at over 60%.^{2,3} However, even after liver resection, HCC often

recurs in the remnant liver and such cases may have a dismal outcome in the early period after surgery.^{1,2} Therefore, selection of patients who would benefit most from surgical treatment is essential for further improvement of outcome.

Recently, there has been increasing evidence that an elevated serum C-reactive protein (CRP) level is associated with poor OS and disease-free survival (DFS) in patients with HCC.⁴⁻⁶ The underlying mechanism is thought to be cancer-related inflammation.⁷⁻⁹ Recent studies have suggested that cancer generates a systemic inflammatory response, resulting in tumor progression, invasion, and metastasis.⁷⁻⁹ CRP is well known to be an inflammatory marker and therefore its use as a surrogate marker of tumor biology has been suggested.¹⁰

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There are some limitations in using the serum CRP level as a marker predictive of survival in cancer patients. In clinical settings, patients will be susceptible to various infections, thus affecting the serum CRP level, in comparison with healthy persons.¹¹ In fact, most patients with HCC have existing liver dysfunction because of chronic hepatitis or liver cirrhosis at the time of diagnosis and are relatively sick in comparison with patients with other diseases.¹ These factors may have a negative impact on the predictive reliability of CRP and moreover some patients may suffer from tumor recurrence and a poor outcome after hepatectomy even if no CRP elevation has been evident. Therefore, some modifications to the use of the serum CRP level may be necessary to predict cancer-related outcomes more precisely. The serum level of alpha-fetoprotein (AFP) is widely used as a marker of HCC and is associated with tumor growth and recurrence.^{12,13} Therefore, measurement of both AFP and CRP may allow more accurate prediction of cancer-related outcomes. Recently, it has been reported that an inflammation-based prognostic system including the serum CRP level can predict the postoperative survival of colorectal patients within the normal range of carcinoembryonic antigen levels.¹⁴ Clinically, we often encounter HCC patients who show a normal level of AFP or a better outcome despite having advanced cancer. CRP may also aid in the prognostication of such patients. Against this background, we attempted to establish a useful scoring system for HCC patients by incorporating the preoperative serum levels of both CRP and AFP, and evaluated its usefulness for prediction of postoperative outcome after hepatectomy.

Methods

A prospectively collected database of 349 patients who underwent initial curative hepatectomy for HCC at Dokkyo Medical University Hospital between April 2000 and March 2012 was analyzed retrospectively. This study was conducted after obtaining approval from the Institutional Review Board of Dokkyo Medical University. Patients lacking laboratory data for CRP and/or AFP on the day of admission were eliminated from the study. To exclude any inflammatory effect, patients who had undergone transileocolic portal vein embolization before hepatectomy, or splenectomy before or simultaneously with hepatectomy, were also eliminated. None of the patients had clinical conditions such as intractable ascites or obstructive jaundice before surgery.

In our department, the Makuuchi criteria are applied for deciding whether hepatectomy for HCC is indicated, which means that patients with uncontrolled ascites or a total bilirubin level of greater than 2 mg/dL are not considered candidates for surgery.^{15,16}

All patients had curative resection with negative margins.

The recommended cut-off values for the preoperative serum CRP and AFP levels were defined by receiver operating characteristic (ROC) curve analysis. ROC curve analysis indicated a serum CRP cut-off value of .29 mg/dL (area under the curve .679, sensitivity .748, specificity .624) and a serum AFP cut-off value of 17.5 ng/mL (area under the curve .625, sensitivity .699, specificity .527). Based on these results, we defined the cut-off value for CRP as .3 mg/dL and that for AFP as 20 ng/mL.

We then constructed a preoperative prognostic scoring system using a serum CRP level of .3 mg/dL and a serum AFP level of 20 ng/mL (the CRP-AFP Score [CAS]). The CAS was defined as follows: CAS 0 ($n = 135$), CRP .3 mg/dL or less and AFP 20 ng/mL or less; CAS 1 ($n = 169$), CRP greater than .3 mg/dL and AFP greater than 20 ng/mL; and CAS 2 ($n = 45$), CRP greater than .3 mg/dL and AFP greater than 20 ng/mL.

SPSS version 17.0 (SPSS, Inc, Chicago, IL) was used to analyze the data. Differences among groups were analyzed using the chi-square test or Kruskal–Wallis test. The OS and DFS were calculated using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. Fifteen variables were assessed in univariate analysis: age (<70 years/ ≥ 70 years), sex (female/male), body mass index (≤ 25 kg/m²/ > 25 kg/m²), HCV antibody (-/+), aspartate aminotransferase (≤ 40 IU/L/ > 40 IU/L), alanine aminotransferase (≤ 40 IU/L/ > 40 IU/L), T-bilirubin (≤ 1 mg/dL/ > 1 mg/dL), prothrombin time ($> 70\%$ / $\leq 70\%$), albumin (≥ 3.5 g/dL/ < 3.5 g/dL), platelet count ($\geq 100,000$ μ L/ $< 100,000$ μ L), CRP ($\leq .3$ mg/dL/ $> .3$ mg/dL), indocyanine green retention rate at 15 minutes (ICG-R15%) ($\leq 10\%$ / $> 10\%$), Child-Pugh class (A/B), AFP (≤ 20 ng/mL/ > 20 ng/mL), and transcatheter arterial embolization (-/+). Multivariate analysis to identify independent risk factors for survival was performed using the Cox proportional hazards model. Statistical differences at P value less than .05 were considered significant.

Results

The background characteristics of the 349 patients who underwent initial curative hepatectomy for HCC are shown in Table 1. There were 274 men and 75 women, 230 patients were HCV antibody positive, 49 were hepatitis B virus surface antigen positive, 68 had an elevated CRP level ($> .3$ mg/dL), 191 had an elevated AFP level (> 20 ng/mL), and 294 were Child-Pugh class A. With regard to clinical background variables, there were no significant correlations of the CAS with age, body mass index, alanine aminotransferase, or use of preoperative transcatheter arterial embolization, whereas significant correlations were observed for sex, HCV antibody positivity, aspartate aminotransferase, total bilirubin, prothrombin time, albumin level, platelet count, ICG-R15%, CRP and AFP levels, and Child-Pugh class.

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