Prognostic impact of soluble intercellular adhesion molecule-1 in hepatocellular carcinoma

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Abstract. The identification of novel biomarkers for hepatocellular carcinoma (HCC) is of great importance in improving the outcome of patients with HCC. The present study aimed to determine the prognostic significance of the soluble intercellular adhesion molecule (sICAM)-1 in patients with HCC. The present study prospectively collected clinicopathological data from 36 patients with HCC who had undergone successful hepatectomy. An analysis using a receiver operating characteristic (ROC) curve was performed to determine the cut-off value for predicting prognosis. Overall survival (OS), recurrence-free survival (RFS) and potential prognostic factors were analyzed. The ROC curve analysis revealed a sICAM-1 cut-off value of 440 ng/ml. HCC patients with sICAM-1 ≥440 ng/ml exhibited a poorer OS and RFS than those with sICAM-1 <440 ng/ml (P=0.002). sICAM-1 ≥440 ng/ml (hazard ratio=3.623; 95% confidence interval: 1.145-11.458; P=0.028) and Child B (hazard ratio=1.514; 95% confidence interval: 1.066-2.150; P=0.021) were independent prognostic factors for OS, and sICAM-1 ≥440 ng/ml was an independent prognostic factor for RFS (hazard ratio=3.625; 95% confidence interval: 1.233-10.659; P=0.019). Serum sICAM-1 may be a promising predictor for the overall and recurrence-free survival of patients with HCC.

Introduction

Hepatocellular carcinoma (HCC), which accounts for 70-85% of the primary liver cancers (1), is the fifth most common cancer and second most common cause of cancer death in men worldwide (2). In 2012 alone, an estimated 782,500 new liver cancer cases were diagnosed, and there were approximately 745,500 deaths due to liver cancer (2). Newly-developed therapeutics using direct-acting antivirals are eradicating most HCVs (3). However, the prognosis of HCC remains poor owing to tumor invasiveness, intra- and extra-hepatic metastasis, multicentric carcinogenesis, and resistance to chemotherapy (4,5). The identification of novel biomarkers for HCC is therefore of great importance in improving the outcome of patients with HCC.

Cellular adhesion molecules, interacting cellular communications, are divided into four groups according to their molecular structures: Cadherins, selectins, integrins, and an immunoglobulin superfamily (6). Intercellular adhesion molecule (ICAM)-1, a member of the immunoglobulin superfamily, is broadly expressed on the membrane of normal tissues, and is selectively expressed in human malignancies (7-10). ICAM-1 is the ligand for the β2-integrins, lymphocyte function-associated antigen (LFA)-1, and Mac-1 (11,12). The expression of ICAM-1 is regulated by locally produced inflammatory cytokines such as IL-1β, tumor necrosis factor α, interleukin (IL)-6, and interferon-γ (13,14). Interestingly, the soluble form of ICAM-1 (sICAM-1) has also been reported to have angiogenic activity (15).

To elucidate the mechanisms of tumor progression in HCC, and to establish certain prognostic markers, we investigated the serum concentration of sICAM-1 and its relationships with inflammatory and nutritional parameters.

Materials and methods

Patients. Thirty-six patients with HCC were enrolled (30 men and six women; mean age, 70.5 years; range, 34 to 84 years) in a prospective setting. In addition, samples from 27 healthy volunteers (10 males and 17 females, mean age, 54.3 years; range 35 to 84 years) were used as controls. Blood samples were collected from the patients between February 2011 and August 2013, before initiation of treatment. Sera from patients were stored at -80˚C until use. All of the patients underwent curative-intent surgery at our department. Following surgery, each patient's final cancer stage was determined pathologically according to the 8th edition of the TNM classification system of malignant tumors published by the Union for International Cancer Control (16). Liver fibrosis stage was determined

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according to the METAVIR score (17). In addition, the Child-Pugh score and indocyanine green retention rate at 15 min (ICGR15) were examined to evaluate liver function. The study protocol was approved by the ethics committee of Fukushima Medical University, and written informed consent was obtained from all enrolled patients and healthy volunteers. Thus, it was designed and conducted in accordance with Good Clinical Practice Guidelines and the latest revision of the Declaration of Helsinki.

Measurements of parameters. The serum concentrations of IL-6, vascular endothelial growth factor, and sICAM-1 were measured using an enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Each sample was used only once after thawing, and not all blood samples were of sufficient volume for all measurements. Patient nutritional status was determined by measuring the serum concentrations of total protein, albumin, retinol binding protein (RBP), transthyretin (TTR), and transferrin, as well as body mass index (BMI) at diagnosis. These parameters were measured at the Central Clinical Laboratory of Fukushima Medical University Hospital. As for the inflammatory parameters, C-reactive protein (CRP), white blood cell count, neutrophil and lymphocyte counts, and the neutrophil-to-lymphocyte ratio (NLR), were used.

Statistical analysis. Data are presented as frequencies or percentages for categorical variables and mean ± standard error for continuous variables, unless otherwise indicated. For categorical clinical variables, differences between the groups were evaluated using Fisher's exact test. The differences in mean values between the groups were analyzed using the Mann-Whitney U test. A receiver operating characteristic (ROC) curve was used to evaluate the usefulness of the examined parameters as a prognostic factor, and associations between two variables were quantified using Spearman's rank correlation coefficient. The mean observation period was 68.5 months (median: 68.7, range: 45.3-83.9), and the final assessment of disease status was made on December 28, 2017. Overall survival (OS) and recurrence-free survival (RFS) were calculated using the Kaplan-Meier method, and differences between the groups were assessed by using the log-rank test. Factors found to be significant in the univariate analysis were subjected to multivariate analysis using a Cox proportional hazard model to identify independent predictors of prognosis. A two-sided P-value of <0.05 was considered statistically significant. All statistical calculations were performed using SPSS® version 24 (IBM Japan, Tokyo, Japan).

Results

Analysis using an ROC curve. Patient characteristics are summarized in Table I. The sICAM-1 serum levels of the HCC patients (median: 438.9 ng/ml, range: 101.1-994.0 ng/ml) were higher than those of the healthy volunteers (median: 207.6 ng/ml, range: 87.8-381.2 ng/ml) (P<0.001; Fig. 1A). In an analysis using a ROC curve (Fig. 1B), the serum sICAM-1 was evaluated as a useful biomarker to predict patient survival (P=0.022), and a sICAM-1 level of 440 ng/dl was determined as the cutoff value. At this cutoff value, sensitivity was 0.737 and specificity was 0.706. Table II shows the patient characteristics according to serum sICAM-1 level. The incidence of ICGR ≥15 was statistically higher in the patients with sICAM-1 ≥440 than in those with sICAM-1 <440 (P<0.001).

Association between sICAM-1 and other parameters. Fig. 2 shows the relationships between serum sICAM-1 levels and other parameters. The serum sICAM-1 levels exhibited statistically significant inverse correlations with TTR (r=−0.379, P=0.023), and showed statistically significant correlations with ICGR15 (r=0.678, P<0.001). However, the serum sICAM-1 showed no correlations with BMI.

Prognostic impact of sICAM-1. The evaluation of the prognostic factors was performed by dividing the patients into two groups for each parameter: Age (<75 years vs. ≥75 years), gender (male vs. female), serum sICAM-1 level (sICAM-1 <440 ng/ml vs. ≥440 ng/ml), T factor (T1 vs. T2), Child-Pugh classification (A vs. B), intrahepatic metastasis (negative vs. positive), vascular invasion (negative vs. positive), and biliary invasion (negative vs. positive). As shown in Fig. 3, the patients with sICAM-1 ≥440 ng/ml showed poorer OS and RFS than those with sICAM-1 <440 ng/ml (P=0.002 and P=0.002, respectively).

Table III summarizes the analyses of a Cox proportional hazard model. With regard to OS, sICAM-1 ≥440 ng/ml, T2, intrahepatic metastasis positive, vascular invasion positive, and biliary invasion positive showed statistical significance in the univariate analysis. sICAM-1 ≥440 ng/ml (hazard ratio: 3.623, 95% confidence interval: 1.145-11.458, P=0.028) and Child B (hazard ratio: 1.514, 95% confidence interval: 1.066-2.150, P=0.021) were independent prognostic factors for OS in the multivariate analysis. With regard to RFS, sICAM-1 ≥440 ng/ml, T2, intrahepatic metastasis positive, vascular invasion positive, and biliary invasion positive showed statistical significance in the univariate analysis. In the multivariate analysis, sICAM-1 ≥440 ng/ml was an independent prognostic factor for the RFS of HCC patients (hazard ratio: 3.625, 95% confidence interval: 1.233-10.659, P=0.019).

Discussion

Immunohistochemically, ICAM-1 is expressed on hepatocytes in cancerous areas but not on hepatocytes in noncancerous areas (18). It has recently been reported that ICAM-1 was a marker of HCC stem cells, and increased numbers of $CD45^{-}ICAM^{+}$ tumor cells in blood samples of HCC patients correlated with worse clinical outcomes (19). On the other hand, circulating sICAM-1 has been reported to be elevated in the serum of patients with various malignancies (20-28). With regard to HCC, Shimizu *et al* reported that sICAM-1 ≥1,000 ng/ml was associated with poor prognosis in HCC patients who had been treated by transcatheter arterial chemoembolization (20), and Zhu *et al* reported that sICAM-1 >684 ng/ml was an independent prognostic factor for OS and RFS in HCC patients who had undergone surgical treatment (21). Our results on the usefulness of sICAM-1 for predicting the survival of HCC patients confirmed their findings; however, our sICAM-1 cutoff threshold of 440 ng/ml was lower than those of the other two studies. With regard

Table I. Patient demographics.

Category	N	(%)
Age		
<75	24	66.7
≥75	12	33.3
Sex		
Male	30	83.3
Female	6	16.7
T		
T1a	8	22.2
T1b	16	44.4
T2	12	33.3
N		
N0	33	91.7
N1	3	8.3
M		
M0	36	100.0
M1	0	0.0
Stage		
IA	8	22.2
IB	16	44.4
II	10	27.8
III	0	0.0
IVA	2	5.6
Operation		
Partial	10	27.8
Segmentectomy	5	13.9
Sectionectomy	7	19.4
Lobectomy	8	22.2
Extended lobectomy	6	16.7

n=36. Partial, partial hepatectomy; TNM, tumor-node-metastasis. T, N and M factors and TNM stage were determined pathologically according to the 8th edition of the TNM classification system of malignant tumors published by the Union for International Cancer Control.

Table II. Patient demographics according to sICAM-1 level.

Characteristics	sICAM-1 <440 (n=18)	sICAM-1 ≥440 (n=18)	P-value
Age			1.000
<75	12	12	
≥75	6	6	
Sex			0.658
Male	14	16	
Female	4	2	
T			0.075
T1	15	9	
T2	3	9	
N			0.229
N0	18	15	
N1	0	3	
Stage			0.229
Stage I-III	18	15	
Stage IV	0	3	
Virus			1.000
-	7	8	
+	11	10	
ICGR15			<0.001[a]
<15	18	7	
≥15	0	11	
PT			0.603
≥70	15	17	
<70	3	1	
Child-Pugh			1.000
A	17	16	
B	1	2	
AFP			0.479
<10.0	8	6	
≥10.0	7	10	
Fibrosis score			0.691
F1-3	15	13	
F4	3	5	
Intrahepatic metastasis			1.000
-	17	8	
+	1	10	
Vascular invasion			0.402
-	16	13	
+	2	5	
Biliary invasion			0.075
-	15	9	
+	3	9	

[a]P<0.05. sICAM-1, soluble form of intercellular adhesion molecule-1; virus, hepatitis B or C virus infection; ICGR15, the retention of indocyanine green after 15 min; T, tumor; N, node; PT, prothrombin time; AFP, α fetoprotein.

to the meanings of higher sICAM-1, it has been reported that sICAM-1 inhibits ICAM-1/LFA-1-mediated cell-to-cell interaction, resulting in tumor cells escaping from cell-mediated immune surveillance (27,29). This escape theory seems possible, considering that a high amount of circulating sICAM-1 was an independent prognostic factor for the RFS in patients with HCC in the present study. Since the source of increased circulating level of the serum sICAM-1 has yet to be elucidated, further investigation will be needed.

We revealed the relationships of serum sICAM-1 levels with the TTR levels and ICGR15. TTR, also known as prealbumin, has a relatively short half-life (approximately two days) and is the earliest laboratory indicator of malnutrition status, as it contains a high percentage of essential amino acids (30). Systemic chronic inflammation has been reported to induce angiogenesis and malnutrition. Thus, higher sICAM-1 might

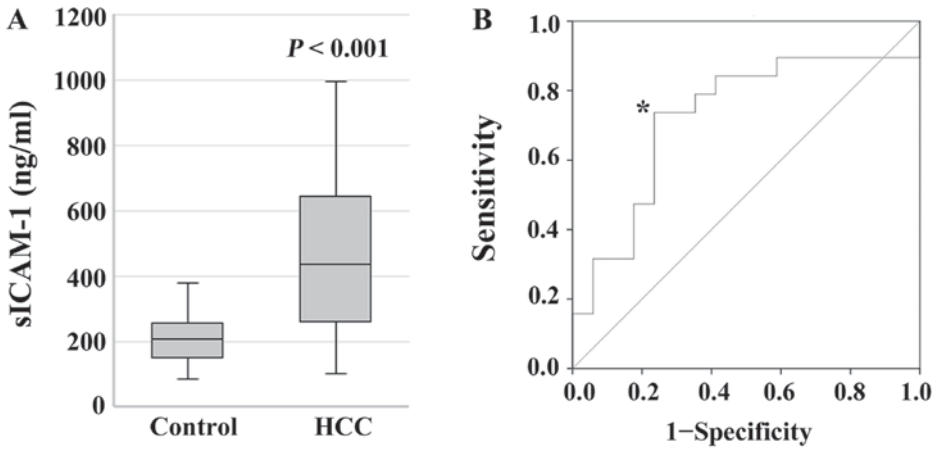

Figure 1. (A) The box-and-whisker plots of sICAM-1. The sICAM-1 serum levels of the patients with HCC (median, 438.9 ng/ml; range, 101.1-994.0 ng/ml) were higher than those of the healthy volunteers (median, 207.6 ng/ml; range, 87.8-381.2 ng/ml; P<0.001). (B) Receiver operating characteristic curve for transthyretin. The calculated area under the curve was 0.724. *The coordinate point when the cut-off threshold of the transthyretin was set to 440 ng/ml. sICAM-1, soluble form of intercellular adhesion molecule 1; HCC, hepatocellular carcinoma.

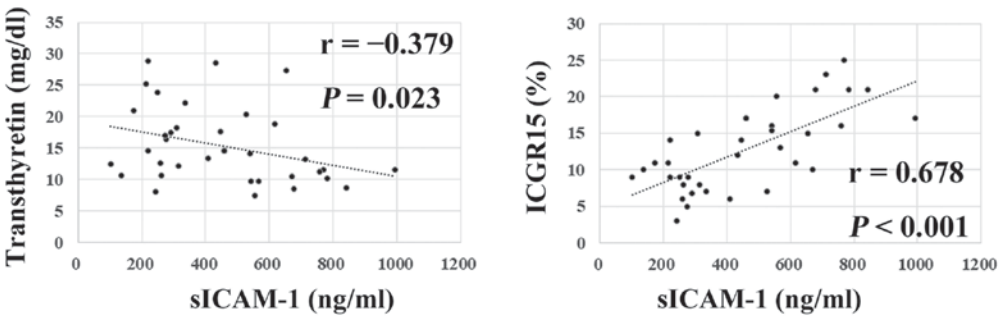

Figure 2. Association between sICAM-1 and other parameters. The sICAM-1 levels exhibited statistically significant inverse correlations with transthyretin (r=-0.379, P=0.023), and exhibited statistically significant correlations with the indocyanine green retention rate at 15 min (ICGR15) (r=0.678, P<0.001). sICAM-1, soluble form of intercellular adhesion molecule 1.

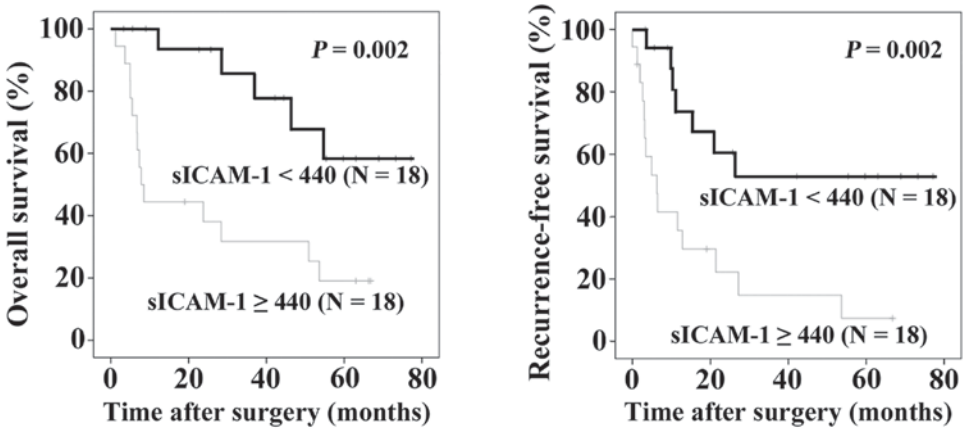

Figure 3. Association between serum sICAM-1 levels and overall and recurrence-free survival. The patients with sICAM-1 ≥440 ng/ml exhibited poorer overall and recurrence-free survival rates than those with sICAM-1 <440 ng/ml (P=0.002 and P=0.002, respectively). sICAM-1, soluble form of intercellular adhesion molecule 1.

be one of the causes of lower serum TTR levels. The meaning of the correlation between sICAM-1 and ICGR15 remains unclear; however, angiogenesis in tumors may prolong the retention of indocyanine green.

There are some limitations to the current study. First is its small sample size. In addition, it is costly and troublesome to examine sICAM-1 in every HCC patient. However, further investigations are warranted whether higher serum sICAM-1 is due to HCC stem cells or circulating tumor cells expressing ICAM-1.

In conclusion, our analysis using a ROC curve revealed that the cutoff value of sICAM-1 for predicting the prognosis

Table III. Cox proportional hazards model.

A, Overall survival

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age <75 vs. ≥75	1.092	0.383-3.116	0.869			
Sex male vs. female	0.622	0.144-2.696	0.526			
sICAM-1 <440 ng/ml vs. ≥440 ng/ml	4.368	1.562-12.216	0.005[a]	3.623	1.145-11.458	0.028[a]
T T1 vs. T2	4.011	1.576-10.210	0.004[a]	0.782	0.148-4.116	0.771
Child-Pugh A vs. B	1.521	1.155-2.003	0.003[a]	1.514	1.066-2.150	0.021[a]
IM negative vs. positive	3.847	1.079-13.719	0.038[a]	0.743	0.119-4.643	0.750
V negative vs. positive	4.063	1.397-11.816	0.010[a]	4.441	0.902-21.864	0.067
B negative vs. positive	2.113	1.087-4.108	0.027[a]	2.594	0.779-8.642	0.121

B, Recurrence-free survival

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age <75 vs. ≥75	1.031	0.416-2.553	0.947			
Sex male vs. female	0.952	0.321-2.823	0.930			
sICAM-1 <440 ng/ml vs. ≥440 ng/ml	3.776	1.528-9.331	0.004[a]	3.625	1.233-10.659	0.019[a]
T T1 vs. T2	6.119	2.389-16.085	<0.001[a]	2.434	0.488-12.135	0.278
Child-Pugh A vs. B	1.371	1.087-1.728	0.003[a]	1.177	0.850-1.629	0.328
IM negative vs. positive	3.553	1.013-12.467	0.048[a]	1.088	0.166-7.120	0.930
V negative vs. positive	2.736	1.024-7.309	0.045[a]	1.142	0.234-5.575	0.870
B negative vs. positive	3.002	1.539-5.858	0.001[a]	2.808	0.906-8.706	0.930

[a]P<0.05. HR, hazards ratio; CI, confidence interval; sICAM-1, soluble form of intercellular adhesion molecule 1; IM, intrahepatic metastasis; T, T factor; V, vascular invasion; B, biliary invasion.

of the HCC patients was 440 ng/ml. The serum sICAM-1 levels in the current study exhibited statistically significant inverse correlations with TTR, and showed statistically significant correlations with ICGR15. The patients with sICAM-1 ≥440 ng/ml showed poorer OS and RFS than those with sICAM-1 <440 ng/ml. Furthermore, sICAM-1 ≥440 ng/ml and Child B were independent prognostic factors for OS, and sICAM-1 ≥440 ng/ml was an independent prognostic factor for RFS in HCC patients.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Authors' contributions

TS and MS contributed to concept, design, and integrity of this study. YF, RO, TI, TK, AK and NS performed data acquisition, analysis, or data interpretation. TS and MS drafted the manuscript and critically revised it for important intellectual content.

Ethics approval and consent to participate

This retrospective study was carried out in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or ethical standards. Written informed consent was obtained from all enrolled patients. All patient data were treated in accordance with the local privacy regulations.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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