

# Correlation Between Preoperative Serum Concentration of Type IV Collagen 7s Domain and Hepatic Failure Following Resection of Hepatocellular Carcinoma

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**Objective:** To determine the predictive value of the preoperative serum concentration of type IV collagen 7s domain (7s collagen) for postoperative hepatic failure in patients undergoing liver resection for hepatocellular carcinoma.

**Summary Background Data:** Clear and reliable criteria for predicting hepatic failure after liver resection are needed. The serum 7s collagen concentration correlates with the histologic degree of active hepatitis and hepatic fibrosis and may predict the regenerative potential of the liver.

**Methods:** Potential risk factors for postoperative hepatic failure, including the serum 7s collagen concentration, were evaluated in 251 patients who underwent liver resection for hepatocellular carcinoma. Prognostic significance was determined by univariate and multivariate analyses.

**Results:** Hepatic failure developed postoperatively in 25 patients, 4 of whom died. The serum 7s collagen concentration correlated with the histologic degree of hepatitis activity and hepatic fibrosis. The serum 7s collagen concentration was a risk factor for postoperative hepatic failure by univariate analysis and was the only risk factor on multivariate analysis. No patient with a serum 7s collagen concentration <12 ng/mL died of postoperative hepatic failure, and all 4 patients who died had a serum 7s collagen concentration  $\geq$ 12 ng/mL.

**Conclusions:** The preoperative serum 7s collagen concentration correlated independently with hepatic failure following liver resection for hepatocellular carcinoma. Patients whose serum 7s collagen is  $\geq$ 12 ng/mL are poor candidates for hepatic resection.

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Improvements in the preoperative assessment of liver function and advances in surgical techniques have reduced morbidity and mortality of liver surgery. However, liver resection in patients with hepatocellular carcinoma (HCC) still results in postoperative hepatic failure and death because most patients with HCC also have chronic liver disease.<sup>1–9</sup> When selecting the therapy for HCC, it is important to know the extent of resection that can be tolerated. Investigators have searched for risk factors that predict postoperative hepatic failure, and various methods have been based on preoperative liver function.<sup>4,5,9–18</sup> Should a patient be deemed a poor operative candidate, locoregional treatment, including percutaneous ethanol injection, microwave coagulation therapy, and radiofrequency ablation therapy, has been developed and used for HCC, especially small HCCs.<sup>19</sup>

Previous studies have shown that hepatic fibrosis and active hepatitis are negative predictive factors for liver regeneration and risk factors for postoperative hepatic failure.<sup>3,9,20–26</sup> It also has been reported that the serum concentration of type IV collagen correlates with the risk of hepatic failure in patients with chronic liver damage.<sup>27</sup> Recently, the type IV collagen 7s domain (7s collagen), involved in connective tissue metabolism, has been identified as a biochemical marker for assessing fibrogenesis and fibrosis in cirrhosis.<sup>28–30</sup> The serum concentration of 7s collagen has been reported to correlate with the severity of active hepatitis and hepatic fibrosis and the magnitude of abnormalities in liver function tests.<sup>29</sup>

In this study, we evaluated a correlation between the preoperative serum 7s collagen concentration and postoperative hepatic failure following hepatic resection, and to serve as a marker for identifying candidates for liver resection for HCC.

## PATIENTS AND METHODS

Since 1994, we have measured the serum 7s collagen concentration in 257 patients with HCC prior to liver resection. Five patients who underwent concomitant resection of a

synchronous second tumor and 1 patient who underwent liver resection and the right atrial tumor thrombectomy requiring extracorporeal circulation were excluded. The remaining 251 patients were the subjects in this study.

The study was conducted in accordance with the Helsinki Declaration and the guidelines of the Ethics Committee of our institution.

### Measurement of 7s Collagen

The serum 7s collagen concentration was measured preoperatively with a commercially available type IV collagen 7s domain radioimmunoassay kit (Diaiatron Co., Tokyo, Japan), which uses a polyclonal antibody against the 7s domain of type IV collagen isolated from human placenta. The reference range of the serum 7s collagen concentration is  $\leq 6$  ng/mL.

### Postoperative Complications

The variables identifying postoperative hepatic failure included hepatic coma with hyperbilirubinemia (total serum bilirubin concentration  $>5$  mg/dL for more than 5 days), intractable pleural effusion or ascites requiring use of diuretics or thoracentesis, or abdominal paracentesis on 2 or more occasions or institution of continuous drainage, or variceal bleeding.<sup>30,31</sup>

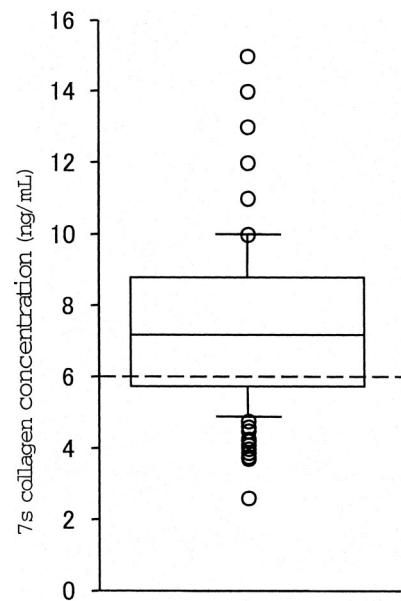
### Pathologic Examination

Surgical specimens were cut into serial slices 5 mm thick, fixed in 10% formalin, and stained with hematoxylin and eosin. The histologic grade of tumor differentiation was assigned using a modification of the classification by Edmonson-Steiner.<sup>32,33</sup> The histologic activity index (HAI) with

**TABLE 1.** Histologic Activity Index Scores

Scores	Description
Histologic activity score (components 1–3)	
0	No activity
1–3	Minimal chronic hepatitis
4–8	Mild chronic hepatitis
9–12	Moderate chronic hepatitis
13–18	Severe chronic hepatitis
Histologic fibrosis score (component 4)	
0	No fibrosis
1	Mild fibrosis (portal fibrous expansion)
2	Moderate fibrosis (bridging fibrosis, portoportal septa)
3	Severe fibrosis (bridging fibrosis, portocentral septa)
4	Cirrhosis

Component 1, periportal necrosis with or without bridging necrosis; component 2, intralobular degeneration and focal necrosis; component 3, portal inflammation.



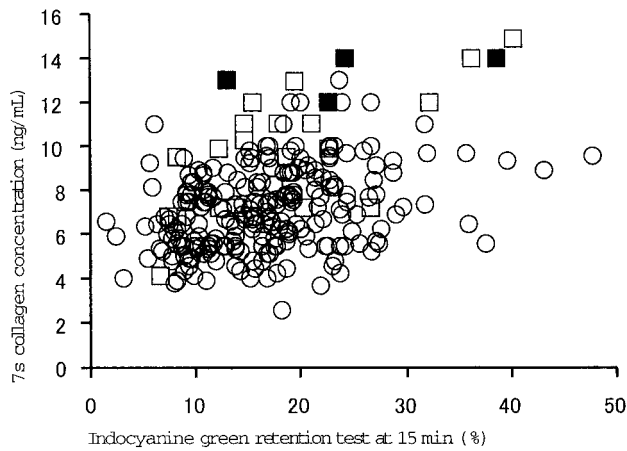
**FIGURE 1.** The serum 7s collagen concentration in patients who underwent liver resection for hepatocellular carcinoma. The serum 7s collagen concentration distributes from 2.6 to 15.0 ng/mL (mean  $\pm$  SD,  $7.4 \pm 2.2$  ng/mL). The reference range of the serum 7s collagen concentration is  $\leq 6.0$  ng/mL (dotted line).

some modifications (Table 1)<sup>34,35</sup> was used to evaluate the severity of active hepatitis (histologic activity score) and the degree of fibrosis (histologic fibrosis score). HAI scores consist of 4 components; component 1, periportal necrosis with or without bridging necrosis; component 2, intralobular degeneration and focal necrosis; component 3, portal inflammation; component 4, fibrosis. HAI scores (components 1–3) of 0 indicated no activity (histologic activity score 0); scores of 1 to 3 indicated minimal activity (histologic activity score 1); scores of 4 to 8 indicated mild activity (histologic activity score 2); scores of 9 to 12 indicated moderate activity (histologic activity score 3); and score of  $\geq 13$  indicated

**TABLE 2.** Correlation Between Serum 7s Collagen Concentration and Results of Other Laboratory Tests

Laboratory Tests	Correlation Coefficient	P
Total bilirubin	0.205	0.0015
ICGR <sub>15</sub>	0.374	$<0.0001$
AST	0.319	$<0.0001$
ALT	0.273	$<0.0001$
Albumin	-0.416	$<0.0001$
Platelet count	-0.428	$<0.0001$

ICGR<sub>15</sub>, indocyanine green retention rate at 15 minutes; AST, aspartate aminotransferase; ALT, alanine aminotransferase.



**FIGURE 2.** The serum 7s collagen concentration in patients with or without postoperative hepatic failure and operative procedure. Major hepatectomy, segmentectomy or greater; minor hepatectomy, smaller than segmentectomy.<sup>37</sup> Circles, patients without postoperative hepatic failure; open squares, patients with postoperative hepatic failure; closed squares, patients who died of postoperative hepatic failure.

severe activity (histologic activity score 4). The degree of fibrosis (histologic fibrosis score) was determined by component 4 of the HAI score. A histologic fibrosis score of 1 indicated portal fibrous expansion, a score of 2 indicated the presence of portal-portal septa without architectural distortion, a score of 3 indicated portocentral septa with architectural distortion, and a score of 4 indicated cirrhosis.

**Statistics**

Student *t* test was used to analyze differences in age and tumor size. The Mann-Whitney *U* test was used to analyze differences in laboratory test results. Fisher exact test or the  $\chi^2$  test was used to compare categoric data between groups. The correlation between the serum 7s collagen concentration and results of other laboratory tests was determined by Pearson's correlation coefficient. The correlation between the serum 7s collagen concentration and the histologic activity score or fibrosis score in noncancerous liver was determined by Spearman's rank correlation. The odds ratio was used to estimate the relative risk for postoperative hepatic failure. Logistic regression analy-

**TABLE 3.** Demographics and Clinicopathologic Features of Patients With and Without Hepatic Failure After Liver Resection

Parameter	Hepatic Failure		P
	No (n = 226)	Yes (n = 25)	
Age (years, mean ± SD)	62.1 ± 7.8	63.4 ± 7.0	0.443
Gender (M:F)	185:41	19:6	0.431
Alcohol abuse	67	8	0.820
History of blood transfusion	52	7	0.620
Anti-HCV	164	20	0.486
HBsAg	36	5	0.587
Diabetes mellitus	35	4	>0.999
Total bilirubin (mg/dL)	0.9 (0.5, 1.3)	0.9 (0.6, 1.4)	0.277
Albumin (g/dL)	3.7 (3.3, 4.1)	3.6 (2.9, 4.0)	0.0195
ICGR <sub>15</sub> (%)	15.5 (7.6, 25.2)	17.9 (7.5, 31.6)	0.179
AST (IU/L)	53 (32, 102)	65 (48, 110)	0.0254
ALT (IU/L)	60 (28, 115)	79 (42, 131)	0.0286
Platelet count (×10 <sup>4</sup> /μL)	14.3 (8.2, 23.2)	11.4 (5.5, 19.9)	0.0029
Prothrombin test (%)	103 (77, 147)	104 (76, 148)	0.994
Type 4 collagen 7s domain (ng/mL)	6.9 (4.8, 9.6)	9.9 (6.4, 14.0)	<0.0001
AFP (>20 ng/mL)	121	17	0.206
Tumor size (cm)	4.0 ± 2.9	4.2 ± 3.0	0.684
Operative procedure (major:minor)	92:134	9:16	0.830
Intraoperative blood loss (g)	800 (280, 2900)	1450 (450, 3650)	0.0050
Time of operation (min)	280 (185, 435)	290 (175, 470)	0.816
Histologic activity score			
0-2	196	16	0.0067
3	30	9	
Histologic fibrosis score			
0-3	134	8	0.0108
4 (cirrhosis)	92	11	

Anti-HCV, anti-hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; ICGR<sub>15</sub>, indocyanine green retention rate at 15 minutes; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein. Results are given as medians, with 10th and 90th percentiles

**TABLE 4.** Risk Factors for Hepatic Failure After Liver Resection for Hepatocellular Carcinoma Calculated by Univariate Analysis

Variable	Odds Ratio	95% CI	P
Age (per 1 year)	1.023	0.966–1.082	0.441
Gender			
Female	1.000		
Male	0.702	0.264–1.867	0.478
Alcohol abuse			
(–)	1.000		
(+)	1.117	0.460–2.713	0.807
History of blood transfusion			
(–)	1.000		
(+)	1.301	0.515–3.286	0.577
Anti-HCV			
(–)	1.000		
(+)	1.512	0.544–4.205	0.428
HBsAg			
(–)	1.000		
(+)	1.005	0.326–3.103	0.993
Diabetes mellitus			
(–)	1.000		
(+)	1.364	0.480–3.876	0.560
AFP			
≤20 ng/mL	1.000		
>20 ng/mL	1.844	0.765–4.446	0.173
Total bilirubin (per 1 mg/dL)	2.085	0.619–7.019	0.236
Albumin (per 1 g/dL)	0.154	0.045–0.522	0.0027
ICGR <sub>15</sub> (per 1%)	1.043	0.992–1.096	0.0979
AST (per 1 IU/L)	1.008	0.999–1.016	0.0757
ALT (per 1 IU/L)	1.008	0.999–1.016	0.0798
Platelet count (per 1 × 10 <sup>4</sup> /μL)	0.907	0.836–0.986	0.0211
Prothrombin test (per 1%)	1.000	0.983–1.018	0.993
Type IV collagen 7s domain (per 1 ng/mL)	1704	1.390–2.088	<0.0001
Operative procedure			
Minor	1.000		
Major	0.825	0.350–1.949	0.661
Intraoperative blood loss (per 1 g)	1.000	1.000–1.000	0.105
Time of operation (per 1 min)	1.001	0.997–1.005	0.514
Histologic activity score			
0–2	1.000		
3	3.675	1.490–9.063	0.0047
Histologic fibrosis score			
1–3	1.000		
4 (cirrhosis)	3.095	1.282–7.472	0.0120

Anti-HCV, anti-hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; ICGR<sub>15</sub>, indocyanine green retention rate at 15 minutes; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein.

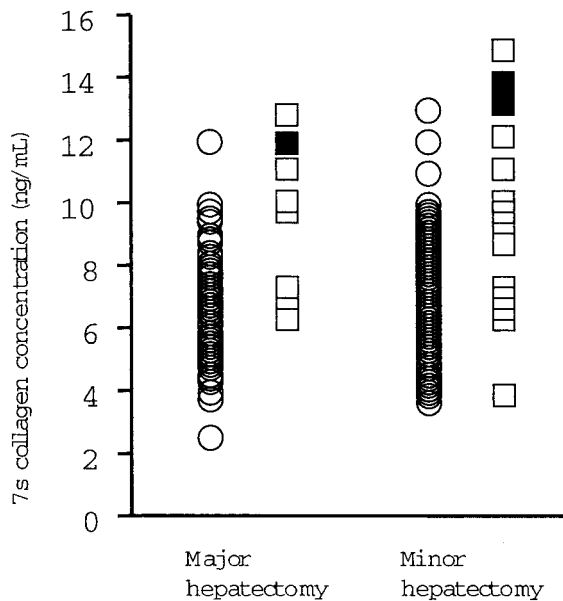
sis was used for univariate analysis. For multivariate analysis, multiple logistic regression analysis was used.

## RESULTS

The 251 patients in this study included 204 men and 47 women. The age range was from 30 to 80 years (mean ± SD, 62.3 ± 7.7 years). A total of 180 patients were positive for

anti-hepatitis C antibody (anti-HCV) alone, 36 patients were positive for hepatitis B surface antigen (HBsAg) alone, 4 patients were positive for both anti-HCV and HBsAg, and 31 patients were negative for both viral markers.

The serum 7s collagen concentration distributed from 2.6 to 15.0 ng/mL (mean ± SD, 7.4 ± 2.2 ng/mL, Fig. 1). Although the serum 7s collagen concentration correlated with



**FIGURE 3.** The correlation between serum 7s collagen concentration and indocyanine green retention rate at 15 minutes. Circles, patients without postoperative hepatic failure; open squares, patients with postoperative hepatic failure; closed squares, patients who died of postoperative hepatic failure.

serum concentration of total bilirubin and albumin, the indocyanine green retention test at 15 minutes (ICGR<sub>15</sub>), serum activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, the *r* values were very low (Table 2, Fig. 2).

The serum 7s collagen concentration correlated with the histologic activity score ( $\rho = 0.271$ ,  $P < 0.0001$ ) and the histologic fibrosis score ( $\rho = 0.437$ ,  $P < 0.0001$ ).

Postoperative hepatic failure developed in 25 patients (hepatic coma with hyperbilirubinemia, 6 patients; intractable pleural effusion or ascites, 24 patients; and variceal bleeding,

1 patient). Four of these patients died of the hepatic failure (hospital death). The clinicopathologic findings were compared in the 226 patients without and the 25 patients with postoperative hepatic failure (Table 3). The groups were similar in age, gender, percentage of patients with a history of alcohol abuse (an estimated daily intake of 86 g ethanol for at least 10 years, according to the criteria of the Liver Cancer Study Group of Japan<sup>36</sup>), diabetes mellitus, blood transfusion, and anti-HCV and HBsAg positivity. Although the serum total bilirubin concentration, the ICGR<sub>15</sub>, and prothrombin test were not different between groups, the serum albumin concentration and the platelet count were lower in patients with than without postoperative hepatic failure. Serum activity of AST and ALT and the serum 7s collagen concentration were higher in patients with than without postoperative hepatic failure. Although no difference was noted in tumor size, operative procedure, or time of operation, intraoperative blood loss was greater in patients who developed postoperative hepatic failure. The percentage of patients with moderate hepatitis activity (histologic activity score 3) or cirrhosis (histologic fibrosis score 4) was greater in patients who developed postoperative hepatic failure.

Table 4 shows the odds ratios (OR) of the possible risk factors for postoperative hepatic failure calculated by univariate analysis. The serum concentration of albumin (OR = 0.154) and 7s collagen (OR = 1.704), the platelet count (OR = 0.907), histologic activity score 3 (OR = 3.675), and cirrhosis (OR = 3.095) were risk factors for postoperative hepatic failure. Activities of AST and ALT were also possible risk factors (OR = 1.008). The serum 7s collagen concentration was significantly higher in patients with postoperative hepatic failure than in patients without the complication in both major hepatectomy (segmentectomy or greater)<sup>37</sup> group and minor hepatectomy (smaller than segmentectomy) group ( $P = 0.0007$  and  $P = 0.0021$ , respectively, Fig. 3). In both groups, the serum 7s collagen concentration in patients who

**TABLE 5.** Risk Factors for Hepatic Failure After Liver Resection for Hepatocellular Carcinoma Calculated by Multivariate Analysis

Variable	Odds Ratio	95% CI	<i>P</i>
Total bilirubin (per 1 g/dL)	1.007	0.209–4.862	0.993
Albumin (per 1 g/dL)	0.368	0.079–1.709	0.202
ICGR <sub>15</sub> (per 1%)	0.972	0.900–1.050	0.468
AST (per 1 IU/L)	0.997	0.977–1.018	0.788
ALT (per 1 IU/L)	1.006	0.987–1.026	0.513
Platelet count (per $1 \times 10^4/\mu\text{L}$ )	1.010	0.929–1.098	0.809
Prothrombin test (per 1%)	1.013	0.993–1.034	0.210
Type IV collagen 7s domain (per 1 ng/mL)	1.727	1.328–2.247	<0.0001

ICGR<sub>15</sub>, indocyanine green retention rate at 15 minutes; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

**TABLE 6.** Results of Laboratory Tests and Operative Methods in Four Patients Who Died of Postoperative Hepatic Failure

Patient no.	Age (year)	T-bil (mg/dL)	Albumin (g/dL)	ICGR <sub>15</sub> (%)	Platelet count ( $\times 10^4/\mu\text{L}$ )	7s Collagen (ng/mL)	Operative methods
1	72	0.3	3.0	37.4	5.9	14.0	Partial
2	62	0.9	3.0	13.0	7.0	13.0	Partial
3	59	1.4	3.8	23.1	17.4	12.0	Rt. lobectomy
4	55	1.3	2.9	26.9	8.0	14.0	Partial

T-bil, total bilirubin; ICGR<sub>15</sub>, indocyanine retention test at 15 min; 7s collagen, type IV collagen 7s domain; partial, partial resection; rt. lobectomy, right lobectomy.

died of the postoperative hepatic failure was  $\geq 12$  ng/mL. The risk of postoperative hepatic failure increased as the serum albumin concentration and platelet count decreased and as AST and ALT activity and the serum 7s collagen concentration increased. The risk of the postoperative hepatic failure was high in patients with moderately active hepatitis or cirrhosis on histopathology. Again, the risk of the postoperative hepatic failure closely correlated with both the severity of active hepatitis and the degree of hepatic fibrosis.

Multivariate analysis was used to estimate the adjusted odds ratio for postoperative hepatic failure based on preoperative data (Table 5). The serum 7s collagen concentration alone was an independent risk factor for postoperative hepatic failure (adjusted OR = 1.727).

The ICGR<sub>15</sub>, which has been used as guidelines for hepatic reserve, ranged from 6.5% to 40.8% in patients with postoperative hepatic failure,<sup>3,5,7,10,17,18,23,26,38-42</sup> whereas the serum 7s collagen concentration in the patients distributed mainly in a relatively high serum concentration of 7s collagen (Fig. 2). The serum 7s collagen concentration was  $\geq 12$  ng/mL in 4 patients who died. The serum concentrations of total bilirubin and albumin, the ICGR<sub>15</sub>, and the platelet count were distributed over wide ranges in these 4 patients (Table 6).

We next divided the subjects into two groups: 1 group included the 237 patients with a low serum 7s collagen concentration (<12 ng/mL) and the other group consisted of the 14 patients with a high serum 7s collagen concentration ( $\geq 12$  ng/mL, Table 7). The incidences of hepatic coma and intractable pleural effusion or ascites were higher among patients with a high serum 7s collagen concentration than patients with a low serum 7s collagen concentration. Variceal bleeding developed in only 1 patient, but this patient had an elevated serum 7s collagen concentration ( $\geq 12$  ng/mL). No patient with a low serum 7s collagen concentration died of postoperative hepatic failure, and all 4 of the patients who died had a high serum 7s collagen concentration.

## DISCUSSION

In this study, the preoperative serum 7s collagen concentration was a risk factor for postoperative hepatic failure by univariate analysis and an independent risk factor by multivariate analysis.

The risk of postoperative hepatic failure correlated closely with both the severity of active hepatitis and the degree of hepatic fibrosis. It is well established that cirrhosis is a risk factor for postoperative hepatic failure.<sup>3,10,13,20,24,43</sup> The degree of hepatic fibrosis is useful as a predictor of liver regeneration and restoration of liver function after liver resection,<sup>44</sup> and it correlates with the risk of postoperative ascites and the duration of postoperative hepatic failure.<sup>9</sup> Several investigators have commented on the role of active hepatitis as a potential risk factor for hepatic failure following liver resection.<sup>9,24</sup> In previous studies, serum transaminase activity was used to determine hepatitis activity. However, the histologic activity of hepatitis does not always correlate with serum transaminase activity, and neither AST and ALT activity was a risk factor by univariate or multivariate analysis. Recently, Eguchi et al<sup>25</sup> emphasized the importance of using histology to evaluate the severity of active hepatitis as a predictor of postoperative hepatic failure. However, it is difficult to obtain noncancerous hepatic tissue from all patients preoperatively, so other less invasive markers are needed. The serum 7s collagen concentration has been re-

**TABLE 7.** Incidence of Hepatic Failure in Patients With a High and Low Concentration of Type IV Collagen 7s Domain

Parameter	Type IV Collagen 7s Domain		P
	<12 ng/mL (n = 237)	$\geq 12$ ng/mL (n = 14)	
Hepatic coma	1	4	<0.0001
Intractable pleural effusion or ascites	16	8	<0.0001
Variceal bleeding	0	1	0.0558
Death due to hepatic failure	0	4	<0.0001

ported to correlate with the severity of active hepatitis, as well as the degree of hepatic fibrosis.<sup>29</sup> We confirmed that the serum 7s collagen concentration correlates with the histologic activity score and the fibrosis score in patients with HCC. Preoperative measurement of the serum 7s collagen concentration informs the surgeon about the severity of active hepatitis and the degree of fibrosis and provides a measure of the risk of postoperative hepatic failure.

Although the indocyanine green clearance test has been used to develop guidelines for hepatic resection, the recommended limit for safe liver resection is different in different series.<sup>3,5,7,10,17,18,23,26,38–42</sup> In this study, the correlation between the serum 7s collagen concentration and the ICGR<sub>15</sub> was weak, and the ICGR<sub>15</sub> ranged widely in patients with postoperative hepatic failure. In addition, the ICGR<sub>15</sub> ranged from 13.0% to 37.4% in patients who died of postoperative hepatic failure, and the ICGR<sub>15</sub> was not a risk factor for the postoperative hepatic failure by either univariate or multivariate analysis. On the other hand, the incidence of hepatic coma and intractable pleural effusion and ascites was higher in patients with an elevated serum 7s collagen concentration. Additionally, the serum 7s collagen concentration was  $\geq 12$  ng/mL in all patients who died of postoperative hepatic failure. No other laboratory tests were risk factors for postoperative hepatic failure by multivariate analysis, although the serum albumin concentration and the platelet count were risk factors by univariate analysis. Thus, preoperative serum 7s collagen concentration seems to be the best available laboratory test for assessing hepatic reserve.

Other reported risk factors for postoperative hepatic failure include age,<sup>10,24</sup> diabetes mellitus,<sup>13</sup> and excessive intraoperative blood loss.<sup>7,13,18,26,43–45</sup> Although excessive intraoperative blood loss was a risk factor by univariate analysis, age and diabetes mellitus were not risk factors in this study.

Limited liver resection has been recommended for patients with cirrhosis.<sup>3,27,45,47</sup> In this study, 4 patients with a serum 7s collagen concentration  $\geq 12$  ng/mL who underwent major hepatectomy (1 patient) or limited resection (partial resection, 3 patients) died of postoperative hepatic failure. Recently, it has been reported that microwave coagulation therapy administered via laparotomy is a less invasive alternative to partial resection.<sup>47</sup> The usefulness of other locoregional therapies, including percutaneous ethanol injection therapy, microwave coagulation therapy, and radiofrequency ablation therapy, has also been reported.<sup>19</sup> Based on our data, patients with a serum 7s collagen concentration  $\geq 12.0$  ng/mL should undergo some treatment other than liver resection. Liver transplantation is another alternative in selected patients with a high serum 7s collagen concentration.

## CONCLUSION

The preoperative serum 7s collagen concentration was correlated with the postoperative hepatic failure, and a con-

centration  $\geq 12$  ng/mL is a relative contraindication to liver resection. Such patients should receive alternative treatment.

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