

# Can the model for end-stage liver disease score replace the indocyanine green clearance test in the selection of right hemihepatectomy in Child-Pugh class A?

Jong Man Kim, Choon Hyuck David Kwon, Jae-Won Joh, Jae Berm Park, Joon Hyeok Lee<sup>1</sup>, Gaab Soo Kim<sup>2</sup>, Sung Joo Kim, Seung Woon Paik<sup>1</sup>

*Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, <sup>1</sup>Division of Gastroenterology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, <sup>2</sup>Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*

**Purpose:** To identify the correlation of the model for end-stage liver disease (MELD) scores with the assessment of the risk of hepatic function after hemihepatectomy in patients with hepatocellular carcinoma (HCC) related to hepatitis B virus (HBV).

**Methods:** A case-control study was performed based on data for 141 consecutive patients who underwent curative right hepatic resection between January 2006 and June 2010.

**Results:** All patients were Child-Pugh class A. The mean age of the patients was 50 years (range, 29–73 years). The group included 114 men (80.9%) and 27 women (19.1%). The distribution of MELD scores (median, 7; range, 6–14) and indocyanine green retention rate at 15 minutes (ICG-R15) (median, 9.2%; range, 1.1%–19.5%) showed no significant correlation ( $P = 0.615$ ). Only one perioperative death (0.7%) occurred within 30 days, which was the result of liver failure by hepatic artery dissection during the Pringle maneuver. Hepatic dysfunction occurred in 25 patients (17.7%) after liver resection. In multivariate analysis, male gender, increased HBV DNA level, and elevated serum aspartate transaminase level were significantly related with hepatic dysfunction. Tumor size and satellite nodule were closely associated with tumor recurrence in HBV-related HCC after right hemihepatectomy and satellite nodule was a predisposing factor for mortality in those patients.

**Conclusion:** MELD score does not accurately predict hepatic function after right hemihepatectomy in patients with resectable HBV-related HCC. MELD scores were not correlated with the ICG-R15 values in patients with Child-Pugh class A. [Ann Surg Treat Res 2014;86(3):122-129]

**Key Words:** Liver disease, Liver function test, Hepatectomy, Hepatocellular carcinoma, Hepatitis B virus

## INTRODUCTION

The management of hepatocellular carcinoma (HCC) is complicated by concurrent primary hepatic malignancy and predisposes patients to chronic liver disease. Hepatic resection presents all the risks of major surgery, even for patients with normal liver function, and limiting conditions for the safety of

hepatic parenchymal resection should reflect the grade of liver dysfunction that is present. Severe cirrhosis arising from viral hepatitis is a major cause of liver dysfunction in patients with primary liver tumors who undergo hepatic resection.

Postoperative liver failure is a serious complication with a high mortality rate; therefore, the goals of hepatic functional assessment in liver surgery are proper patient selection and

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**Corresponding Author: Jae-Won Joh**

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea

**Tel:** +82-2-3410-3466, **Fax:** +82-2-3410-0040

**E-mail:** jw.joh@samsung.com

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the prediction of the safety limits of the hepatic parenchymal resection rate. Various methods have been advocated to evaluate hepatic function reserve before operation. Efforts to assess patients' postoperative course have almost exclusively been limited to preoperative evaluations, but the liver is a multifunctional organ and thus a single comprehensive liver function test does not exist. Biochemical blood tests (e.g., serum bilirubin, prothrombin time index, albumin levels) combined with clinical risk measures such as the Child-Turcotte-Pugh (CTP) class [1], the model for end-stage liver disease (MELD) score [2], and the Makuuchi criteria [3] provide useful estimates of liver function and reserve.

The Makuuchi criteria using the indocyanine green (ICG) clearance test have been used in Eastern Asian countries including Korea, Japan, and China. However, ICG clearance tests have not shown reliable results because the ICG clearance test was influenced by hepatic blood flow [4]. Additionally, the ICG clearance test may vary depending on the examiner. However, the MELD score suggests objective results.

Data are lacking on the preoperative use of the MELD score as an early predictor of outcome in patients with hepatitis B virus (HBV)-related HCC who have undergone right hemihepatectomy. We evaluated the feasibility of using MELD scores for the selection of hemihepatectomy. Thus, the aim of the present study was to identify the correlation between MELD scores and assessment of hepatic function after hemihepatectomy in these patients.

## METHODS

### Patients

We reviewed the data for 141 patients with HBV-related HCC who underwent curative right hepatic resection at Samsung Medical Center between January 2006 and June 2010. We excluded patients younger than 18 years, those with pathological portal vein invasion and/or bile duct invasion, those with pathologically proven mixed HCC or cholangiocarcinoma, and those who were lost to follow-up after right hemihepatectomy. The demographics, preoperative laboratory analyses, and pathologic data of all patients were retrieved from electronic medical records and were retrospectively reviewed. Liver function was evaluated by the Child-Pugh classification system. None of the patients in either group received postoperative adjuvant therapy before recurrence was detected.

### Surgery and pathology

Before surgery, each patient underwent conventional liver function tests, measurement of the ICG retention rate at 15 minutes (ICG-R15), and MELD scores. Preoperative tests of liver function included serum bilirubin, transaminases, alkaline

phosphatase, albumin, and prothrombin time. HBV screening was done by measurement of the hepatitis B surface antigen. The levels of  $\alpha$ -fetoprotein (AFP) and protein induced by vitamin K absence/antagonism-II (PIVKA-II) were also measured in all patients. Selection criteria for the liver resection procedure depended on tumor location and extent, liver function, ICG test, and future liver remnant volume. In patients without ascites and with normal bilirubin levels, ICG-R15 became the main determinant of resectability. Right hepatic resection was judged to be feasible when ICG-R15 was less than 20% [3]. Child-Pugh class C, severe comorbidity, and distant metastasis were considered contraindications for right hemihepatectomy.

Standard operative techniques for right hemihepatectomy were used. Adequate mobilization was performed depending on the part of liver to be resected. Selective clamping of the portal vein and hepatic artery was performed when feasible; if the clamping was not feasible, the intermittent Pringle maneuver was performed. Parenchymal transection was performed using a Cavitron Ultrasonic Surgical Aspirator (CUSA) under low central venous pressure. Only one senior pathologist reviewed each specimen for histologic confirmation of the diagnosis. Postoperative histological assessments and reporting included tumor diameter, cirrhosis, encapsulation, satellite nodule, and microvascular invasion of HCC. Histologic grade of HCC was assessed according to the Edmonson-Steiner system [5], as well differentiated (grade I), moderately differentiated (grade II), or poorly differentiated (grades III, IV). Hepatic fibrosis was assessed by the Ludwig-Batts scoring system and accordingly graded on a scale of 0–4 (F0, absent; F1, portal fibrosis; F2, periportal fibrosis; F3, bridging fibrosis; F4, cirrhosis). Cirrhosis was defined as the presence of stage 4 fibrosis.

### Postoperative morbidity and mortality

Perioperative and postoperative complications and mortality were recorded to assess the morbidity and mortality of right hemihepatectomy. Morbidity was defined as the development of one or more postoperative complications. Complications were defined as postsurgical events related to the surgery. These included massive ascites, pulmonary complications, wound problems, and bile leakage. Hepatic dysfunction was defined as prolonged hyperbilirubinemia (serum total bilirubin level  $\geq 6$  mg/dL) and massive ascites requiring diuretics after liver resection. Postoperative mortality was defined as death within 30 days of right hemihepatectomy.

### Statistical analysis

All data were analyzed using IBM SPSS ver. 21 (IBM Co., Armonk, NY, USA). Continuous variables are presented as median and range, and were compared using the Mann-Whitney U test. Categorical variables were compared by Fisher exact test, as appropriate. Multivariate analysis of hepatic dysfunction was

performed using binary logistic regression. Patient survival and recurrence were calculated using the Kaplan-Meier method. The predictors of tumor recurrence in univariate analysis were performed using the Cox regression hazard model. Clinical and pathological variables that were found to show prognostic significance in univariate analysis were entered into a Cox multivariate proportional hazards model to determine which factors were independently predictive of HCC recurrence. A value of  $P < 0.05$  was considered statistically significant.

## RESULTS

### Patient characteristics

One hundred forty-one patients with a diagnosis of HCC related to HBV infection underwent curative liver resection. The median age of the patients was 50 years (range, 29–73 years). The number of men was 114 (80.9%) and the number of

women was 27 (19.1%). All patients were Child-Pugh class A and all were treated with right hepatic resection. Table 1 presents the demographics and preoperative laboratory results. Median MELD scores and ICG-R15 values were 7 points (range, 6–14) and 9.2% (range, 1.1%–19.5%), respectively. The median AFP and PIVKA-II levels were 47.9 IU/mL (range, 1–200,000 IU/mL) and 217 mAU/mL (range, 5–1,200 mAU/mL), respectively. Eighteen patients (12.8%) received antiviral therapy for HBV infection prior to liver resection.

Pathologic results and postoperative complications are summarized in Table 2. The median tumor size was 5.5 cm (range, 0.8–17.5 cm) and the median free resection margin was 10 mm (range, 2–70 mm). Liver cirrhosis was present in 51 patients (36.3%). Most patients had microvascular invasion ( $n = 99$ , 70.2%). Only one perioperative death (0.6%) occurred within 30 days, and was the result of liver failure following hepatic artery dissection during the Pringle maneuver. Hepatic dysfunction occurred in 25 patients (17.7%) after liver resection. Pulmonary complications, such as atelectasis, pneumonia, pleural effusion, and pneumothorax, were the main

**Table 1.** Demographic features and preoperative laboratory findings in patients with HBV-related hepatocellular carcinoma

Variable	Value
Gender	
Male	114 (80.9)
Female	27 (19.1)
Age (yr)	50 (29–73)
Medical history	
Diabetes	20 (14.2)
Hypertension	27 (19.1)
Cerebrovascular accidents	2 (1.4)
Tuberculosis	5 (3.5)
Others	2 (1.4)
White blood cell ( $\mu\text{L}$ )	5,680 (1,820–12,950)
Hemoglobin (g/dL)	14.1 (9.3–18.8)
Platelet ( $\mu\text{L}$ )	175,000 (40,000–627,000)
INR	1.07 (0.91–1.32)
Albumin (g/dL)	4.1 (2.9–5.1)
Total bilirubin (mg/dL)	0.7 (0.2–4.3)
AST (IU/L)	39 (14–353)
ALT (IU/L)	39 (7–385)
ALP (IU/L)	84 (40–282)
Creatinine (mg/dL)	0.90 (0.56–1.67)
MELD score	7 (6–14)
ICG-R15 (%)	9.2 (1.1–19.5)
AFP $\geq 200$ (ng/mL)	47 (33.3)
PIVKA-II $\geq 200$ (mAU/mL)	65 (46.1)
HBV DNA (log) $\geq 5$	37 (26.2)
HBeAg-positive	28 (19.9)
Preoperative antiviral therapy	18 (12.8)

Values are presented as number (%) or median (range).

INR, international normalized ratio; MELD, model for end-stage liver disease; ICG-R15, indocyanine green retention rate at 15 minutes; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonism-II.

**Table 2.** Pathological features and postoperative complications in patients who underwent hepatic resection

Variable	Value
Pathologic features	
Tumor size (cm)	5.5 (0.8–17.5)
Grade (3 and 4)	13 (9.2)
Encapsulation	119 (84.4)
Microvascular invasion	99 (70.2)
Satellite nodule	48 (34.0)
Cirrhosis	51 (36.25)
Free resection margin (mm)	10 (2–70)
Postoperative morbidity and mortality	
Complications	
Wound	27 (19.1)
Atelectasis	52 (36.9)
Pneumonia	6 (4.3)
Pleural effusion	8 (5.7)
Bile leakage	10 (7.1)
Ascites requiring diuretics	15 (10.6)
Bleeding	1 (0.7)
Diarrhea	2 (1.4)
Delirium	2 (1.4)
Hematuria	1 (0.7)
Ileus	2 (1.4)
Hepatic encephalopathy	1 (0.7)
Poor blood glucose control	28 (19.8)
Pneumothorax	1 (0.7)
Portal vein thrombosis	1 (0.7)
Hepatic dysfunction	25 (17.7)
Postoperative mortality	1 (0.7)
Hospitalization (day)	10 (3–68)

Values are presented as median (range) or number (%).

postsurgical complications. Fifteen patients (10.6%) developed ascites that required prolonged diuretic therapy and 27 patients (19.1%) had documented wound infections. Ten patients (7.1%) developed bilomas or intra-abdominal collections that required radiology-guided percutaneous drainage. Mean hospitalization after liver resection was 10 days (range, 3–68 days).

### Predictors of hepatic dysfunction

Univariate analysis showed that elevated HBV DNA levels, low total bilirubin level, and the presence of microvascular invasion were associated with hepatic dysfunction after curative liver resection (Table 3). No other variables differed

significantly between the two groups. On multivariate analysis, male gender, and increased HBV DNA level and serum aspartate transaminase levels were significantly associated with hepatic dysfunction (Table 4).

### Relation between ICG-R15 and MELD score

ICG-R15 and MELD scores prior to liver resection showed no correlation ( $r = 0.044$ ,  $P = 0.615$ ) (Fig. 1) and there were no statistically significant differences in ICG-R15 between a low MELD score (6 points) and a high MELD score (10 points) (Fig. 1). Median ICG-R15 in cirrhotic and noncirrhotic patients was 9.8% (range, 1.1%–19.5%) and 8.7% (range, 1.4%–18.1%), respectively.

**Table 3.** Factors associated with hepatic dysfunction after hepatic resection

Variable	No hepatic dysfunction (n = 116)	Hepatic dysfunction (n = 25)	P-value
Male gender	97 (83.6)	17 (68.0)	0.092
Age (yr)	50 (29–73)	50 (32–67)	0.957
Medical history			
Diabetes	16 (13.8)	4 (16.0)	0.756
Hypertension	23 (19.8)	4 (16.0)	0.785
Cerebrovascular accidents	2 (1.7)	0 (0)	0.508
Tuberculosis	5 (4.3)	0 (0)	0.586
White blood cell (μL)	5,795 (1,820–12,950)	4,740 (3,100–9,450)	0.055
Hemoglobin (g/dL)	14.3 (9.3–18.8)	13.6 (10.8–15.5)	0.115
Platelet (μL)	174,000 (40,000–627,000)	182,000 (82,000–314,000)	0.551
INR	1.07 (0.91–1.32)	1.07 (0.94–1.25)	0.914
Albumin (g/dL)	4.1 (2.9–5.1)	4.1 (3.5–4.8)	0.727
Total bilirubin (mg/dL)	0.7 (0.2–4.3)	0.6 (0.2–1.2)	0.028
AST (IU/L)	37.5 (14–283)	49 (22–353)	0.091
ALT (IU/L)	37 (7–288)	43 (8–385)	0.491
ALP (IU/L)	84 (41–228)	84 (40–282)	0.490
Creatinine (mg/dL)	0.9 (0.58–1.67)	0.79 (0.56–1.13)	0.009
MELD score	7 (6–14)	7 (6–9)	0.499
ICG-R15 (%)	9.3 (1.1–19.5)	8.0 (1.1–19.3)	0.463
AFP ≥ 200 (ng/mL)	40 (34.5)	7 (29.2)	0.813
PIVKA-II ≥ 200 (mAU/mL)	54 (50.0)	11 (52.4)	0.842
Tumor size (cm)	53 (8–175)	56 (19–125)	0.683
Grade (3 and 4)	10 (8.6)	3 (12.0)	0.702
Encapsulation	96 (83.5)	23 (92.0)	0.367
Microvascular invasion	77 (66.4)	22 (88.0)	0.032
Satellite nodule	35 (30.2)	13 (52.0)	0.061
Cirrhosis	42 (36.2)	9 (36.0)	0.984
HBV DNA (log) ≥ 5	26 (23.4)	11 (45.8)	0.041

Values are presented as number (%) or median (range).

INR, international normalized ratio; MELD, model for end-stage liver disease; ICG-R15, indocyanine green retention rate at 15 minutes; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonism-II.

**Table 4.** Risk factors for hepatic dysfunction by multivariate analysis

Variable	Odds ratio	95% Confidence interval	P-value
Male gender	54.566	2.483–1,198.970	0.011
HBV DNA (log) ≥ 5	24.608	1.264–479.223	0.034
AST	1.095	1.009–1.187	0.030

There was no statistically significant difference in ICG-R15 between patients with cirrhosis and without. However, MELD scores in cirrhotic patients were higher than in non-cirrhotic patients (8 points vs. 7 points;  $P = 0.026$ ). Additionally, there were no differences in ICG-R15 and MELD scores between patients with hepatic dysfunction and without hepatic dysfunction (Table 4).

### Risk factors for HCC recurrence and survival

The mean follow-up duration of patients was 28.7 months after liver resection (range, 1–69 months) and ninety-one patients (64.5%) received antiviral therapy. The 1-, 2-, and 3-year disease free survival rate and overall survival rate were 61.4%, 54.0%, and 49.5% and 87.7%, 77.6%, and 71.7%, respectively (Fig. 2). HCC recurrence was detected in sixty-eight patients (48.2%). The recurrent sites of most patients were the intrahepatic site ( $n = 31$ , 45.6%), extrahepatic site ( $n = 9$ , 13.2%), and the intrahepatic and systemic sites concurrently ( $n = 28$ , 41.2%). On

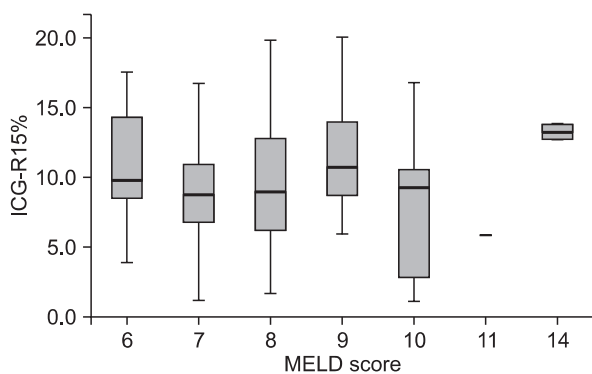
multivariate analysis, tumor size  $\geq 5$  cm, AFP  $\geq 200$  ng/mL, increased ALP levels, and satellite nodule were predisposing factors for tumor recurrence (Table 5). In addition, tumor size  $\geq 5$  cm, increased ALP levels, and satellite nodule were closely associated with overall survival after liver resection (Table 6).

## DISCUSSION

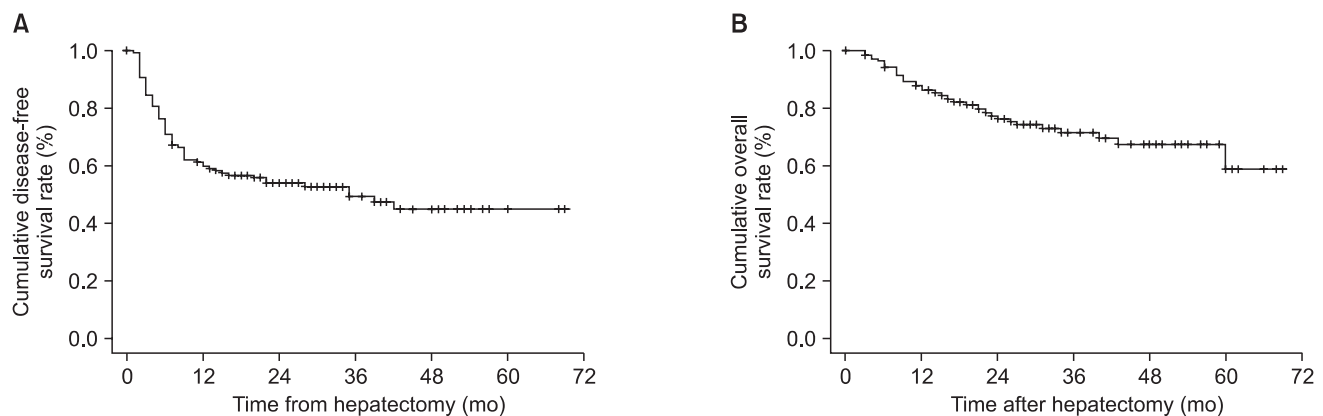
For patients with HCC, but with limited disease (Barcelona Clinic Liver Cancer stage A/B) and relatively preserved liver function, surgical resection presents a potentially curative treatment [6]. However, resection is associated with significant risks of perioperative morbidity and liver dysfunction depending on the extent of the coexisting liver disease. In planning treatment for individual patients with HCC, a reliable or validated risk stratification scheme is essential; HCC develops by diverse etiologies, and these may lead to diverse outcomes after hepatic resection. Current preoperative testing protocols may not support a reliable risk stratification scheme for patients with HCC. We conducted this study of patients with HBV-related HCC who underwent right hepatic resection with the aim of correcting the bias of etiology and operation.

In Eastern countries, ICG test results are routinely combined with CTP scores to evaluate liver function; however, the ICG test is not as well-accepted in Western countries. A decision tree for the hepatectomy procedure, proposed by Makuuchi et al. [3], is based on only three parameters: the presence or absence of uncontrolled ascites, the serum bilirubin level, and the ICG-R15. The extent of the hepatectomy procedure is based on the ICG-R15 value. This is the one surgical algorithm that is the one most widely accepted in Korea and has led to significant reductions in operative mortality and morbidity among patients with HCC. With use of the Makuuchi criteria, hepatic resection may be performed with almost zero mortality [3,7].

ICG is a synthetic dye that is eliminated by the liver without



**Fig. 1.** ICG-R15 and MELD scores prior to right hemihepatectomy showed no correlation in patients with HBV-related HCC ( $r = 0.044$ ,  $P = 0.615$ ). ICG-R15, indocyanine green retention rate at 15 minutes; MELD, model for end-stage liver disease.



**Fig. 2.** Cumulative disease-free survival (A) and overall survival (B) in patients after right hemihepatectomy.

**Table 5.** Risk factors for HCC recurrence after right hemihepatectomy in patients with HBV-related HCC

Variable	Odds ratio	95% Confidence interval	P-value
Univariate			
Female gender	1.001	0.546–1.833	0.988
Age	0.969	0.941–0.999	0.041
HBeAg positive	1.194	0.616–2.316	0.600
HBV DNA (log) $\geq$ 5	1.465	0.861–2.491	0.159
AFP $\geq$ 200 ng/mL	2.991	1.844–4.850	0.000
PIVKA-II $\geq$ 200 mAU/mL	2.010	1.194–3.382	0.009
AST	1.007	1.003–1.011	0.001
ALT	1.005	1.002–1.009	0.004
ALP	1.008	1.003–1.013	0.003
MELD score	0.929	0.765–1.128	0.456
ICG-R15	1.043	0.980–1.110	0.188
Tumor size $\geq$ 5 cm	3.306	1.936–5.642	0.000
Encapsulation	0.607	0.331–1.116	0.108
Microvascular invasion	3.085	1.613–5.901	0.001
Free resection margin	0.996	0.979–1.012	0.603
Cirrhosis	1.253	0.770–2.039	0.363
Preoperative antiviral treatments	0.756	0.346–1.654	0.484
Postoperative antiviral treatments	0.720	0.289–1.790	0.479
Satellite nodule	2.409	1.490–3.898	0.000
Hepatic dysfunction	1.310	0.725–2.366	0.371
Multivariate			
AFP $\geq$ 200 ng/mL	1.864	1.018–3.413	0.044
ALP	1.009	1.002–1.016	0.009
Satellite nodule	2.674	1.505–4.753	0.001
Tumor $\geq$ 5 cm	2.763	1.462–5.222	0.002

HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonism-II; MELD, model for end-stage liver disease; ICG-R15, indocyanine green retention rate at 15 minutes.

extrahepatic metabolism or excretion because it is not reabsorbed in the intestine and therefore avoids enterohepatic recirculation. Biliary ICG excretion correlates with decreased hepatic adenosine triphosphate concentration [8], and this reduction in hepatic energy status may correspond to decreased regenerative capacity after surgery. Thus, clearance of ICG from the blood has been applied to determine the peri- and postoperative risk before hepatectomy [9]. Studies of liver function before hepatectomy using the ICG clearance test indicate a relationship between preoperative ICG clearance test results and postoperative outcomes [9-11]. Normal ICG retention at 15 minutes ranges from 8% to 14% [12]. However, the ICG clearance test does not show true parenchymal function as hepatic blood flow may substantially influence the ICG test [4].

The Makuuchi criteria were applied to the treatment of all patients in our study [3], and no patients had exceptionally high bilirubin levels or uncontrollable ascites. Our results also showed that patients with CTP class A experienced near-zero mortality after right hemihepatectomy. The ICG-R15 values among patients in the present study ranged from 1.1% to 19.5%, indicating a broad range in the severity of underlying liver disease. These results indicate that hepatic resection can be

safely performed in patients who meet the Makuuchi criteria.

The MELD score has emerged as a useful tool for estimating mortality in patients awaiting liver transplantation and has been applied in the allocation of donor livers [2,13]. The MELD score shows a significant correlation with the degree of metabolic liver functional impairment, and an increase in the MELD score is associated with a decrease in residual liver function [14]. Thus, the MELD score has been applied to predict the postoperative mortality risk of patients undergoing hepatic resection in Western countries [15,16]. Patients with a MELD score  $\geq$ 14 have a significantly increased risk of morbidity and poor outcome postabdominal surgery [15]. This recent data has led some authors to suggest that the MELD score be used in place of the Child-Pugh score in assessing the feasibility of surgery for patients with chronic liver disease.

Some studies have reported that a MELD score  $\geq$ 9 independently predicts mortality after resection of HCC [16,17]. Cucchetti et al. [18] showed that cirrhotic patients with a MELD score  $\geq$ 11 may have a high risk of postoperative liver failure. Notably, however, MELD score may not accurately predict postoperative mortality in patients without cirrhosis [19,20]. The MELD score in that study (median, 7; range, 6–14) was not

**Table 6.** Risk factors for mortality after right hemihepatectomy in patients with HBV-related hepatocellular carcinoma

Variable	Odds ratio	95% Confidence interval	P-value
Univariate			
Female gender	1.638	0.767–3.496	0.202
Age	0.988	0.951–1.027	0.545
HBeAg positive	0.792	0.292–2.151	0.648
HBV DNA (log) $\geq$ 5	1.258	0.604–2.620	0.541
AFP $\geq$ 200 ng/mL	2.454	1.274–4.726	0.007
PIVKA-II $\geq$ 200 mAU/mL	2.347	1.095–5.031	0.028
AST	1.007	1.003–1.012	0.002
ALT	1.007	1.003–1.011	0.002
ALP	1.007	1.001–1.013	0.028
MELD score	0.937	0.726–1.211	0.620
ICG-R15	1.057	0.971–1.150	0.200
Tumor size $\geq$ 5 cm	3.759	1.715–8.236	0.001
Grade (3 and 4)	2.055	0.856–4.937	0.107
Encapsulation	0.448	0.211–0.951	0.036
Microvascular invasion	9.625	2.311–40.092	0.002
Free resection margin	0.991	0.967–1.016	0.494
Cirrhosis	0.978	0.498–1.921	0.948
Preoperative antiviral treatments	0.926	0.327–2.622	0.885
Postoperative antiviral treatments	0.206	0.000–5.638	0.043
Satellite nodule	5.017	2.537–9.922	0.000
Hepatic dysfunction	1.365	0.622–2.995	0.438
Multivariate			
ALP	1.010	1.001–1.018	0.022
Satellite nodule	6.940	2.980–16.158	0.000
Tumor $\geq$ 5 cm	4.649	1.765–12.242	0.002

AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonism-II; MELD, model for end-stage liver disease; ICG-R15, indocyanine green retention rate at 15 minutes.

significantly related to mortality [19]. In a consecutive series of patients with and without cirrhosis, who underwent hepatic resection for HCC, MELD score failed to predict postoperative outcomes in those patients who did not have cirrhosis [20]. In the present study, median MELD scores were very low (7 points) and MELD scores of most patients were less than 10 points. The MELD scores of cirrhotic patients were higher than that of noncirrhotic patients (8 points vs. 7 points,  $P = 0.026$ ). However, there was no statistically significant difference in MELD scores between patients with hepatic dysfunction and without. In this study, MELD scores and ICG-R15 of patients with HBV-related HCC were not associated with hepatic dysfunction after right hemihepatectomy. Presumably, the majority of patients undergoing elective right hemihepatectomy have a low MELD score compared with patients undergoing liver transplantation. This suggests that MELD scores predict surgical outcomes only for patients with advanced liver cirrhosis.

The ICG clearance test and the MELD score both show high sensitivity in evaluating liver function; hence, a clinical relationship between them might be expected. This study investigated the correlation between ICG clearance values and MELD scores in HBV-related HCC patients who underwent

right hemihepatectomy. However, the relation between the two parameters showed no significant correlation, possibly because both parameters had a narrow range.

The present study had several limitations. First, this study included a relatively small number of patients, resulting in a lack of statistical power to correlate mortality with ICG-R15 or MELD score. Second, we cannot exclude the possibility of selection bias in excluding patients with significantly elevated ICG retention who might have benefited from surgery because ICG-R15 was used in the clinical assessment of patients before surgery. Third, the population of enrolled patients was so healthy that clinical laboratory values in most patients were within the normal range. Therefore, no patients died during the abbreviated follow-up period.

In conclusion, selection criteria for parenchymal resection in HBV-related HCC may be safely based on the ICG-R15 score. However, the MELD score does not accurately predict hepatic function after right hemihepatectomy in this group of patients. The MELD score was not correlated with the ICG-R15 value in patients with Child-Pugh class A. In the future, the prospective safety of hepatic resection may be preferentially based on ICG-R15 values, in lieu of MELD scores. As mortality following

right hemihepatectomy approaches zero, prospective trials of preoperative hepatic testing can no longer be planned with mortality as an endpoint.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## REFERENCES

1. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-9.
2. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464-70.
3. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. *Semin Surg Oncol* 1993;9:298-304.
4. Schneider PD. Preoperative assessment of liver function. *Surg Clin North Am* 2004;84:355-73.
5. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 1954;7:462-503.
6. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. *Surgery* 2007;141:330-9.
7. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003;138:1198-206.
8. Chijiwa K, Watanabe M, Nakano K, Noshiro H, Tanaka M. Biliary indocyanine green excretion as a predictor of hepatic adenosine triphosphate levels in patients with obstructive jaundice. *Am J Surg* 2000;179:161-6.
9. Hsieh CB, Chen CJ, Chen TW, Yu JC, Shen KL, Chang TM, et al. Accuracy of indocyanine green pulse spectrophotometry clearance test for liver function prediction in transplanted patients. *World J Gastroenterol* 2004;10:2394-6.
10. Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. *Hepatol Res* 2009;39:107-16.
11. Mullin EJ, Metcalfe MS, Maddern GJ. How much liver resection is too much? *Am J Surg* 2005;190:87-97.
12. Lam CM, Fan ST, Lo CM, Wong J. Major hepatectomy for hepatocellular carcinoma in patients with an unsatisfactory indocyanine green clearance test. *Br J Surg* 1999;86:1012-7.
13. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003;124:91-6.
14. Botta F, Giannini E, Romagnoli P, Fasoli A, Malfatti F, Chiarbonello B, et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. *Gut* 2003;52:134-9.
15. Befeler AS, Palmer DE, Hoffman M, Longo W, Solomon H, Di Bisceglie AM. The safety of intra-abdominal surgery in patients with cirrhosis: model for end-stage liver disease score is superior to Child-Turcotte-Pugh classification in predicting outcome. *Arch Surg* 2005;140:650-4.
16. Delis SG, Bakoyiannis A, Dervenis C, Tassopoulos N. Perioperative risk assessment for hepatocellular carcinoma by using the MELD score. *J Gastrointest Surg* 2009;13:2268-75.
17. Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. *J Gastrointest Surg* 2005;9:1207-15.
18. Cucchetti A, Ercolani G, Cescon M, Ravaioli M, Zanella M, Del Gaudio M, et al. Recovery from liver failure after hepatectomy for hepatocellular carcinoma in cirrhosis: meaning of the model for end-stage liver disease. *J Am Coll Surg* 2006;203:670-6.
19. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006;243:373-9.
20. Teh SH, Sheppard BC, Schwartz J, Orloff SL. Model for end-stage liver disease score fails to predict perioperative outcome after hepatic resection for hepatocellular carcinoma in patients without cirrhosis. *Am J Surg* 2008;195:697-701.