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Validation for models for tumor recurrence after liver transplantation in hepatectomy patients

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Purpose: Early recurrence of hepatocellular carcinoma (HCC) remains a challenging issue after hepatic resection (HR) because of the associated poor prognosis. Models for tumor recurrence after liver transplantation (MoRAL) have been designed to predict tumor recurrence in HCC patients in the liver transplantation setting. This study aimed to validate the predictability of MoRAL for HCC recurrence or patient death and to evaluate the predictors of early HCC recurrence in hepatectomy patients with treatment-naïve solitary HCC.

Methods: This study included 443 patients with HCC recurrence after HR from January 2005 to December 2011. Patients were stratified into early recurrence (n = 312) and late recurrence (n = 131) groups according to the development of recurrence either within or more than 2 years after hepatectomy.

Results: The median levels of alpha-fetoprotein and protein induced by vitamin K absence-II and the median MoRAL score were significantly higher in the early recurrence group than in the late recurrence group. Regarding pathologic characteristics, the median tumor size, prevalence of tumor grade 3 or 4, microvascular invasion, presence of tumor necrosis, and macrovascular invasion in the early recurrence group were greater than those in the late recurrence group. Multivariate analysis showed that tumor grade 3 or 4, microvascular invasion, and high preoperative MoRAL score were predisposing factors for early HCC recurrence after HR.

Conclusion: The MoRAL score can be used to predict early recurrence in patients with HCC who undergo curative HR. Using this model, other treatments could be considered for patients with early recurrence predicted after HR.
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Key Words: Biochemical tumor markers, Hepatocellular carcinoma, Neoplasm recurrence, Prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide [1,2]. Although various treatment strategies have been developed for HCC, hepatic resection (HR) is considered the initial curative treatment strategy for HCC, along with liver transplantation (LT) in especially early HCC [3]. However, HCC recurrence after HR is the primary limitation reducing the effectiveness of HCC treatment because of its high incidence [4]. In particular, early recurrence leads to a worse survival rate among patients [5,6].

Traditionally, serum tumor markers including α-FP and

protein induced by vitamin K absence-II (PIVKA-II) have been considered monitoring factors or potential predictors of poor prognosis after multimodal treatments for HCC as they are indirect indicators of tumor aggressiveness [7-10].

A tumor recurrence prediction model based on a combination of PIVKA-II and α-FP for HCC patients after living donor LT (LDLT) beyond the Milan criteria was previously introduced for predicting HCC recurrence [11]. The models for tumor recurrence after liver transplantation (MoRAL) score ($11 \times \sqrt{PIVKA-II} + 2 \times \sqrt{\alpha-FP}$) employs 2 tumor markers [11]. A previous study reported that a low MoRAL score (<314.8 points) was closely associated with better recurrence-free survival and overall survival after LDLT compared with a high MoRAL score because MoRAL score reflects tumor aggressiveness and biology [11].

However, no study employing the MoRAL score in HR in HCC patients has been reported. On the basis of the usefulness of the MoRAL score in predicting tumor aggressiveness, we hypothesized that the MoRAL score can predict patient prognosis following HR for treatment-naïve solitary HCC. The purpose of this study is to validate the predictability of MoRAL for HCC recurrence or patient death and to evaluate the predictors of early HCC recurrence after HR in patients with treatment-naïve solitary HCC.

METHODS

Patients

This study included patients with recurrent HCC after HR, which was diagnosed on the basis of several guidelines and histologically confirmed after HR at Seoul National University Hospital (SNUH; n = 938) or Samsung Medical Center (SMC; n = 1,382) from January 2005 to December 2011 [12,13].

This study was approved by the Institutional Review Boards (IRBs) at 2 participating centers (No. 1807-084-959 from SNUH and No. 2019-09-063-003 from SMC). The need for informed consent was waived by the IRBs because of the retrospective investigation.

Solitary HCC patients with Child-Pugh class A and pre-operative α-FP and PIVKA-II records who underwent curative HR were included. Patients with the following characteristics were excluded: no preoperative data on either α-FP or PIVKA-II, R1 resection, ruptured HCC, non-Korean status, history of malignancy other than HCC, under 18 years of age, history of adjuvant therapy after HR, or loss to follow-up after HR. Finally, 443 patients were identified for inclusion in our study. Patient medical information was retrospectively investigated.

Definition

The early recurrence group was defined as patients with HCC recurrence within 2 years after HR and the late recurrence group was defined as patients with HCC recurrence more than 2 years after HR. Surgical HR of more than 3 segments was defined as major resection. In addition, when HCC recurrence was diagnosed by radiologic imaging, the presence of 10 or more intrahepatic tumor numbers was defined as diffuse intrahepatic tumor recurrence.

Surgery and surveillance

The surgical procedure of HR and the histological evaluation of specimens have been previously described [8,9]. All patients who underwent HR visited outpatient services one month after their surgery and then every 2 or 3 months thereafter. At the outpatient visit, the patients were evaluated for blood tests, liver function tests, α-FP, PIVKA-II, and radiologic tests. Liver CT and liver MRI were alternately examined every 3 months for 2 years after surgery.

Treatment of recurrence

When HCC recurrence was detected during follow-up after HR, patients were treated within 2 months after HCC recurrence. Solitary intrahepatic recurrent HCC patients with Child-Pugh class A underwent re-resection. Radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) was considered in cases of solitary HCC measuring less than 3 cm when re-resection was difficult or dangerous to conduct. Transarterial chemoembolization (TACE) was considered when multiple intrahepatic recurrences were detected or when re-resection, RFA, or PEI was difficult. Salvage LDLT was considered if decompensated liver function and potential living liver donors were present. Combined TACE and RFA (TACE-RFA) was performed in SMC in intrahepatic small solitary HCC when the approach of the percutaneous RFA needle was difficult due to tumor location. Systemic chemotherapy was not initially considered as a treatment in patients with intrahepatic HCC recurrence.

Statistical analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are described as medians and ranges. Comparisons of categorical variables were performed using the chi-square test or Fisher exact test. The Mann-Whitney U-test was used for continuous variables. Disease-free survival (DFS) was considered as the period from the operation date to HCC recurrence date, and patient survival (PS) was defined as the period from the operation date to death date. Survival rates were analyzed using the Kaplan-Meier method with a log-rank test. All significant predictors of early recurrence in bivariate analysis were analyzed in a binary logistic regression model to show independent values by multivariate analysis. All tests were 2-sided, and statistical significance was defined as P < 0.05. All statistical analyses

were performed using IBM SPSS Statistics ver. 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

The baseline characteristics of the early and late recurrence groups are summarized in Table 1. Of the 443 study participants, 312 (70.4%) were included in the early recurrence group. Median α-FP and PIVKA-II levels were 61 ng/mL (range, 2–356,800 ng/mL) and 143 mAU/mL (range, 2–48,000 mAU/mL), respectively, in the early recurrence group and 12 ng/mL (range, 2–21,137 ng/mL) and 44 mAU/mL (range, 2–9,030 mAU/mL) in the late recurrence group. Accordingly, the median MoRAL score in the early recurrence group was significantly higher than that in the late recurrence group (182.8 points *vs.* 97.2 points, P < 0.001). There were no significant differences in sex, age, etiology, body mass index, hemoglobin concentration,

Table 1. Baseline characteristics between early and late recurrence groups

Characteristic	Early recurrence group (n = 312)	Late recurrence group (n = 131)	P-value
No. of patients	312	131	
Age (yr)	54 (19–82)	57 (34–81)	0.092
Male sex	260 (83.3)	107 (81.7)	0.680
Etiology			0.726
HBV	254 (81.4)	107 (81.7)	
HCV	12 (3.8)	8 (6.1)	
NBNC	5 (1.6)	2 (1.5)	
Alcohol	3 (1.0)	2 (1.5)	
Others	38 (12.2)	12 (9.2)	
Body mass index (kg/m^2)	24.2 (16.7–31.2)	23.6 (14.7–36.3)	0.212
Hemoglobin (g/dL)	14.3 (8.1–17.7)	14.4 (7.0–17.8)	0.218
Platelet (/μL)	152,500 (13,900–547,000)	148,000 (12,800–298,000)	0.240
Total bilirubin (mg/dL)	0.8 (0.2–2.0)	0.8 (0.3–1.9)	0.233
AST (IU/L)	37 (7–466)	34 (10–225)	0.072
ALT (IU/L)	38 (8–290)	35 (7–186)	0.119
Albumin (g/dL)	4.1 (2.8–5.1)	4.1 (3.1–5.0)	0.307
Creatinine (mg/dL)	0.9 (0.4–7.3)	0.9 (0.6–5.6)	0.625
INR	1.09 (0.13–1.28)	1.09 (0.76–1.36)	0.668
α-FP, ≥40 ng/mL	169 (54.2)	49 (37.4)	0.002
PIVKA-II, ≥100 mAU/mL	117 (37.5)	45 (34.4)	<0.001
ICG-R15 (%)	10.2 (0.3–73.5)	11.3 (0.3–49.0)	0.512
MoRAL score, >314.8 points	89 (28.5)	12 (9.2)	<0.001

Values are presented as number only, median (range), or number (%).
NBNC, non-hepatitis B and non-hepatitis C; INR, international normalized ratio; PIVKA-II, proteins induced by vitamin K absence-II; ICG-R15, indocyanine green clearance rate at 15 minutes; MoRAL, model to predict the tumor recurrence after living donor liver transplantation.

Table 2. Perioperative and pathologic characteristics

Characteristic	Early recurrence group (n = 312)	Late recurrence group (n = 131)	P-value
Major resection	104 (33.3)	33 (25.2)	0.093
Tumor size (cm)	4.1 (1.0–21.0)	3.0 (1.1–12.0)	<0.001
Tumor grade 3 or 4	140 (44.9)	32 (24.4)	<0.001
Tumor hemorrhage	149 (47.4)	51 (38.9)	0.079
Tumor necrosis	178 (57.1)	54 (41.2)	0.003
Microvascular invasion	187 (59.9)	48 (36.6)	<0.001
Macrovascular invasion	23 (7.4)	0 (0)	0.001
Intrahepatic metastasis	37 (11.9)	10 (7.6)	0.095
Beyond Milan criteria based on pathology	138 (44.2)	29 (22.1)	<0.001
Hospital stay (day)	10 (5–92)	9 (6–33)	0.201

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

platelet count, international normalized ratio, AST level, ALT level, albumin level, total bilirubin level, creatinine level, and indocyanine green retention rate at 15 minutes between the 2 groups.

Perioperative and pathologic characteristics

The perioperative and pathologic characteristics of the early and late recurrence groups are outlined in Table 2. The median tumor size and prevalence of tumor grade 3 or 4 in the early recurrence group were significantly greater than those in the late recurrence group. Also, the presence of tumor necrosis in the resected tumor, microvascular invasion, and portal vein tumor thrombosis were significantly more frequent in the early recurrence group than in the late recurrence group. Accordingly,
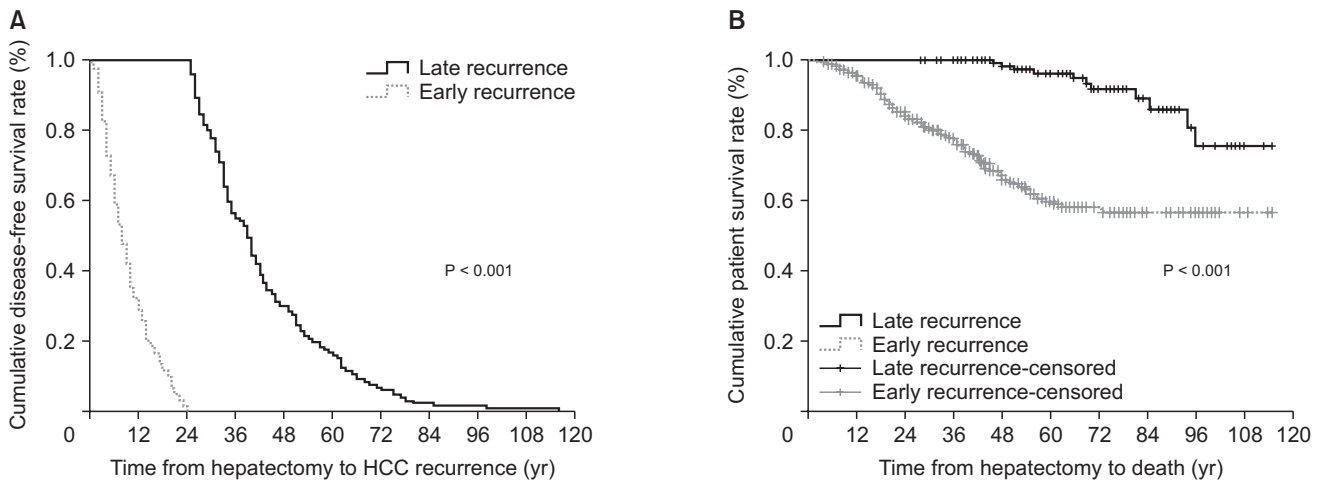

Fig. 1. Comparison of hepatocellular carcinoma (HCC) recurrence and death after hepatic resection between early and late recurrence groups.

Table 3. Characteristics at HCC recurrence

Characteristic	Early recurrence group (n = 312)	Late recurrence group (n = 131)	P-value
First HCC recurrence			
Time from HR to first HCC recurrence (mo)	8 (1–24)	39 (25–116)	<0.001
Tumor size at 1st HCC recurrence (cm)	1.5 (0.5–9.2)	1.3 (0.2–3.8)	0.089
α-FP at first HCC recurrence (ng/mL)	9 (1–200,000)	4 (2–15,912)	<0.001
PIVKA-II at first HCC recurrence (mAU/mL)	25 (8–24,000)	22 (9–699)	0.018
MoRAL score at first HCC recurrence	62.6 (34.0–1,786.2)	57.1 (35.8–297.4)	0.001
Extrahepatic recurrence	3 (1.0)	1 (0.8)	0.841
Diffuse intrahepatic recurrence	21 (6.7)	2 (1.5)	0.032
Beyond Milan criteria	62 (19.9)	10 (7.6)	0.001
Treatments			0.031
TACE	184 (59.0)	58 (44.3)	
RFA	74 (23.7)	47 (35.9)	
PEI	12 (3.8)	4 (3.1)	
Re-resection	22 (7.1)	16 (12.2)	
LDLT	13 (4.2)	2 (1.5)	
Others	1 (0.3)	1 (0.8)	
TACE and RFA	6 (1.9)	3 (2.3)	
Second HCC recurrence			
Time from first to second HCC recurrence (mo)	13 (1–110)	17 (1–73)	0.359
Extrahepatic recurrence at 2nd recurrence	6 (1.9)	1 (0.8)	0.679
Follow-up after HR (mo)	37 (4–115)	68 (28–115)	<0.001

Values are presented as number (%) or median (range).
HCC, hepatocellular carcinoma; HR, hepatic resection; PIVKA-II, proteins induced by vitamin K absence-II; MoRAL, model to predict the tumor recurrence after living donor liver transplantation; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; LDLT, living donor liver transplantation.

the proportion of cases beyond Milan criteria based on pathology in the early recurrence group was higher than that in the late recurrence group (44.2% *vs.* 22.1%, P < 0.001). There were no significant differences in the incidence of major resection, the presence of tumor hemorrhage, intrahepatic metastasis, or hospitalization between the 2 groups.

Hepatocellular carcinoma recurrence and survival

The median follow-up duration after HR for treatment-naïve solitary HCC was significantly shorter in the early recurrence group (37 months *vs.* 68 months, P < 0.001). Both DFS and PS were worse in the early recurrence group than in the late recurrence group (P < 0.001 and P < 0.001, respectively) (Fig. 1). The median time from HR to first HCC recurrence was 8 months (range, 1–24 months) in the early recurrence group and 39 months (range, 25–116 months) in the late recurrence group (Table 3).

When HCC recurrence was diagnosed, the median α-FP level, PIVKA-II level, and MoRAL score were significantly higher in the early recurrence group than in the late recurrence group. Accordingly, the incidence of a MoRAL score greater than 314.8 points was 14.1% in the early recurrence group (n = 29) but

0% in the late recurrence group. Patients with MoRAL scores greater than 314.8 points before HR presented worse DFS and PS compared with patients with MoRAL scores of 314.8 points or less (Fig. 2). The incidence rates of diffuse intrahepatic recurrence and beyond Milan criteria based radiologic images were also higher in the early recurrence group than in the late recurrence group (6.7% *vs.* 1.5%, P = 0.032). TACE was widely used in both groups as a treatment for recurrent HCC, but RFA or re-resection was more often used in the late recurrence group than in the early recurrence group.

Multivariate analysis revealed that tumor grade 3 or 4, microvascular invasion, and MoRAL score greater than 314.8 points before HR were strongly associated with early HCC recurrence following curative HR in solitary treatment-naïve HCC patients (Table 4).

There were no statistically significant differences in the median time from first HCC recurrence to second HCC recurrence and presence of extrahepatic recurrence between the 2 groups. However, DFS from first HCC recurrence to second HCC recurrence and PS from first HCC recurrence to death were significantly worse in the early recurrence group and in patients with MoRAL score greater than 314.8 points before HR lower than in the late recurrence group or in patients with MoRAL score of 314.8 points or less before HR (Figs. 3, 4).

DISCUSSION

The present study revealed that a preoperative MoRAL score greater than 314.8 points is closely associated with worse DFS and PS and can predict early recurrence. The time from first HCC recurrence to second HCC recurrence and the time from first HCC recurrence to patient death were correlated with a preoperative MoRAL score greater than 314.8 points.
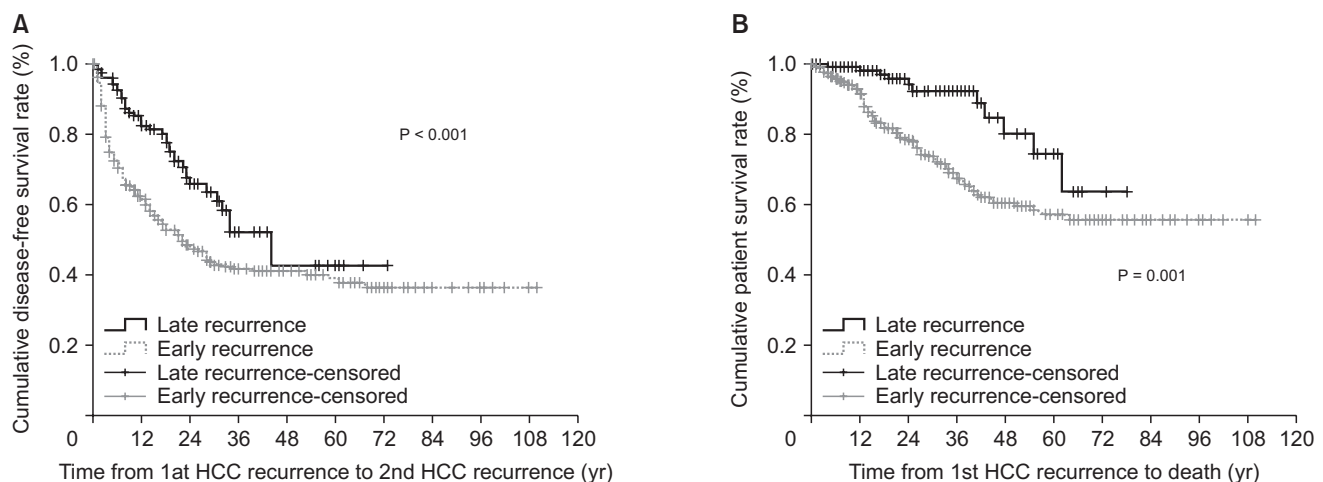
Table 4. Risk factors for early recurrence within 2 years after curative liver resection

Risk factor	OR (95% CI)	P-value
Tumor grade 3 or 4	2.069 (1.277–3.351)	0.003
Tumor size, >5 cm	1.495 (0.870–2.568)	0.146
Tumor necrosis	1.240 (0.792–1.943)	0.347
Microvascular invasion	1.712 (1.077–2.722)	0.023
MoRAL score, >314.8 points	2.229 (1.093–4.547)	0.027

OR, odds ratio; CI, confidence interval; MoRAL, model to predict the tumor recurrence after living donor liver transplantation.

Fig. 2. Comparison of hepatocellular carcinoma (HCC) recurrence and death from first HCC recurrence between the early and late recurrence groups.

Preoperative serum α-FP level is a prognostic factor correlated with oncological outcomes [11]. The expression of α-FP in HCC tissues was shown to be closely associated with biological aggressiveness and tumor differentiation of HCC because the serum α-FP level reflects tumor necrosis and tumor cell proliferation or regeneration of the underlying liver [14,15].

PIVKA-II level for detection or diagnosis of HCC has been demonstrated and widely used in Asian countries, but experiences using PIVKA-II as a screening diagnostic tool in European countries remain limited in number [14]. PIVKA-II has been proven to act not only as a diagnostic biomarker but also as an independent prognostic factor in HCC patients [8-10]. Also, PIVKA-II has been reported to be another independently predisposing factor of intrahepatic recurrence; a high serum PIVKA-II level was closely associated with tumor recurrence by intrahepatic metastasis of tumor cells via the portal vein

because of the increased biological invasiveness to the vessel [16]. Thus, serum PIVKA-II has been demonstrated to be strongly associated with extrahepatic metastasis and microvascular invasion, even in early HCC [17,18].

These observations suggest that serum α-FP and PIVKA levels have a significant association with a high rate of HCC recurrence after surgery [8-10]. Our study also demonstrated that the early recurrence group presented significantly higher preoperative α-FP and PIVKA-II levels than the late recurrence group. Early recurrence of HCC is known to shorten the survival time after HR [6], which implies that early recurrent HCC cases are biologically more aggressive than late recurrent HCC cases [14].

The MoRAL score is a model that involves PIVKA-II and α-FP as components. Accordingly, MoRAL scores in the early recurrence group were significantly higher than those in the
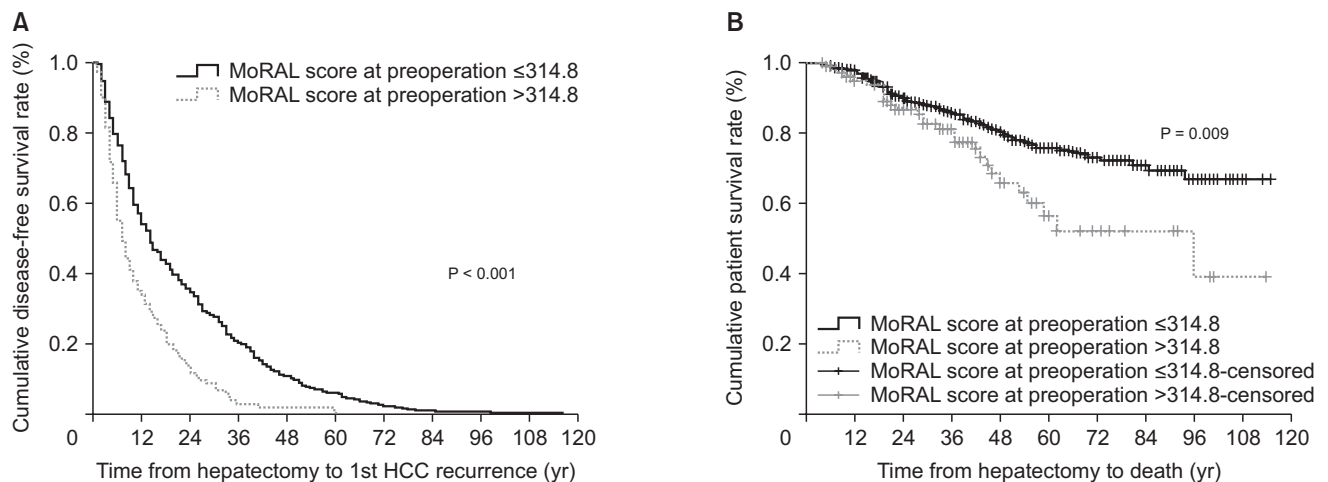

Fig. 3. Comparison of hepatocellular carcinoma (HCC) recurrence and death after hepatic resection according to the models for tumor recurrence after liver transplantation (MoRAL) score.
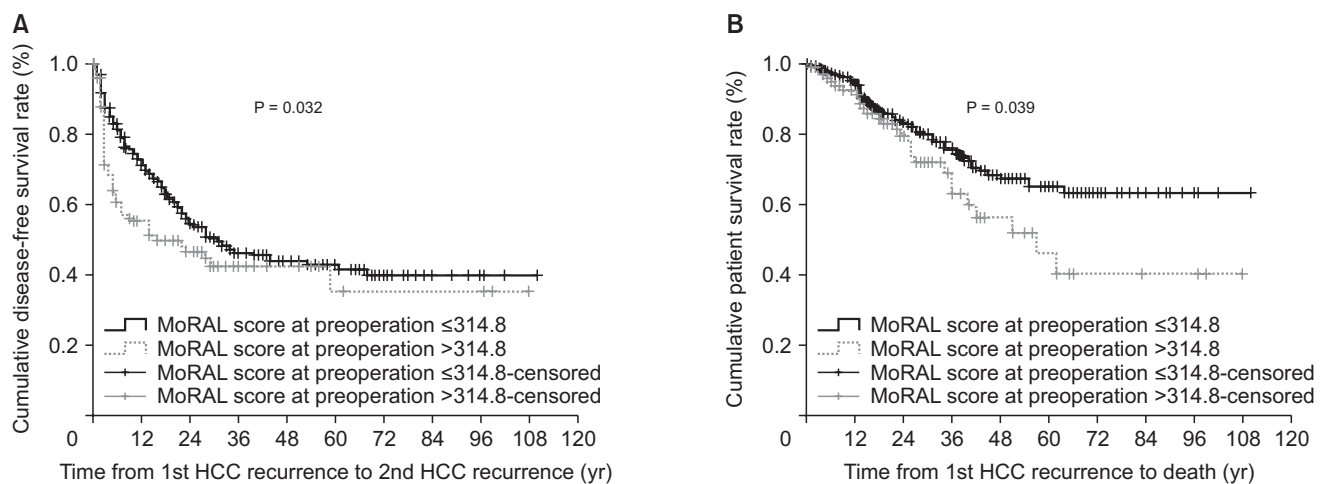

Fig. 4. Comparison of hepatocellular carcinoma (HCC) recurrence and death from first HCC recurrence according to the models for tumor recurrence after liver transplantation (MoRAL) score.

late recurrence group. The MoRAL score was developed for predicting early recurrence after LDLT in HCC patients [11]. Clinicians could use this approach to identify patients beyond the Milan criteria who are at low risk of tumor recurrence after LDLT. Higher MoRAL scores are associated with cytokeratin 19 expression, which is a stemness-related marker and indicates tumor aggressiveness or tumor invasiveness [15]. A previous study reported that a low MoRAL score (<314.8 points) was closely associated with a significantly lower risk of both tumor recurrence and overall death than was a high MoRAL score (>314.8 points) [19]. Therefore, the predictability and statistical usefulness of the MoRAL score were demonstrated in an LT setting [20]. Recently, another study validated use of the MoRAL score in RFA patients [21]. However, LDLT is not always an option in solitary HCC patients [12]. If liver function is preserved and adequate living liver donors are not available, HR is more highly recommended than LDLT in patients with solitary HCC. In our study, the MoRAL score was significantly associated with DFS and PS after HR. Our study also demonstrated that high MoRAL scores were consistent with the findings of previous studies [11,19,21]. The cut-off value of 314.8 points was statistically useful in the case of HR as was true in the case of LDLT. The MoRAL score was statistically meaningful not only in univariate analysis but also in multivariate analysis. Interestingly, the MoRAL score can predict the development of early HCC recurrence within 2 years after HR. In addition, a high MoRAL score predicted early recurrence within 2 years after HR and the chance for the second recurrence after the first recurrence.

The biggest factor that impacts survival after treatment of HCC is early recurrence, based on the present study. Appropriate treatments for early recurrence improve the survival rate of patients [5]. Using the MoRAL score model, we can discern patients in the early recurrence risk group in the preoperative stage. Therefore, we cautiously suggest that regular or frequent surveillance for the development of early recurrence by liver radiologic images might be necessary among patients with high MoRAL scores. The risk of developing early recurrence after HR for treatment-naïve solitary HCC seemed to be quite high among patients with high MoRAL scores. Early detection of early recurrent HCC improves the survival rate by facilitating the earlier introduction of appropriate treatments such as PEI, RFA, TACE, re-resection, and LDLT [5].

Our study has several limitations. First, there is a potential risk for selection bias because of its retrospective design. In addition, our study included only recurrent hepatectomy patients with HCC. Second, as our study population reflects the epidemiology of HCC in South Korea, most of our patients had chronic hepatitis B. Third, it was not easy to gather detailed information from 2 hospitals. The type of liver resection, intraoperative blood loss and transfusion during the surgical procedure, and postoperative complications were not investigated. Further studies validating the prognostic role of the MoRAL score in HCC patients with different etiologies in Western countries are warranted to generalize our results.

In conclusion, we validated the MoRAL score for prediction of oncological outcome after HR in patients with treatment-naïve solitary HCC. Patients with MoRAL scores of 314.8 points or less demonstrated better outcomes in comparison with patients with high MoRAL scores. Patients with high MoRAL scores (>314.8 points) might require frequent regular surveillance regarding the development of early tumor recurrence, and MoRAL scoring is an easily performed, widely available, objective, and reproducible means by which to identify patients at greater potential risk of recurrence.

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