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Comparison of 10 noninvasive models for predicting overall survival in patients with intermediate-stage hepatocellular carcinoma

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Abstract

Intermediate-stage hepatocellular carcinoma (HCC) is heterogeneous in terms of tumor size, number, and effects on liver function. Various noninvasive models have been proposed to assess functional hepatic reserve or fibrosis severity in patients with HCC. This study assessed the feasibility of 10 noninvasive models and compared their prognostic ability for patients with intermediate-stage HCC.

This study retrospectively enrolled 493 patients with intermediate-stage HCC who received treatment at China Medical University Hospital from January 2012 to November 2018. Demographic data, clinical features, and factors associated with overall survival (OS) were recorded at baseline. Receiver-operating characteristic curve analysis and the DeLong method were respectively employed to evaluate and compare the models' OS prediction performance.

Of the 493 patients, 373 (75.7%) were male, and 275 (55.8%) had liver cirrhosis (LC). The median age was 64 years (interquartile range: 55–72). Most patients had tumor volume ≤50% (n = 424, 86.0%), and the maximum tumor size was 6.0 (4.0–8.5) cm. The median α-fetoprotein was 36.25 (6.13–552.91) ng/mL. The patients underwent transarterial chemoembolization (TACE, n = 349) or surgery (n = 144). The median follow-up period was 26.07 (9.77–48.27) months. Across the 10 models, the albumin–bilirubin (ALBI) score had the highest area under the receiver operating characteristic curve (AUROC) (0.644, 95% confidence interval: 0.595–0.693) in all patients. In subgroup analyses, the Lok index, platelet–albumin–bilirubin score, ALBI score, and Lok index had the highest AUROC values in patients without cirrhosis, with cirrhosis, undergoing TACE, and undergoing surgery, respectively. Multivariate Cox regression analysis revealed that independent predictors of longer OS were ALBI grade 1 in all patients, patients with LC, and patients undergoing TACE and Lok index grade 1 in patients without LC and patients undergoing surgery.

Among the 10 noninvasive models, ALBI score exhibited the highest diagnostic value in predicting OS for all patients, patients with cirrhosis, and those undergoing TACE, and Lok index grade exhibited the highest diagnostic value in predicting OS in patients without cirrhosis and those undergoing surgery.

Abbreviations: AFP = α-fetoprotein, ALBI = albumin–bilirubin, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio, AST = aspartate aminotransferase, AUROC = area under receiver operating characteristic curve, BCLC = Barcelona Clinic Liver Cancer, CDS = cirrhosis discriminant index, CLIP = Cancer of the Liver Italian Program, CT = computed tomography, GUCI = Göteborg University cirrhosis index, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, INR = international normalized ratio, LC = liver cirrhosis, MRI = magnetic resonance imaging, OS = overall survival, PALBI = platelet–albumin–bilirubin, RFA = radiofrequency ablation, ROC = receiver-operating characteristic, TACE = transarterial chemoembolization.

Keywords: albumin–bilirubin (ALBI) grade, intermediate-stage hepatocellular carcinoma, Lok grade, noninvasive model

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1. Introduction

Hepatocellular carcinoma (HCC) is a critical health problem worldwide,[1] accounting for >700,000 deaths per year.[2] HCC typically develops alongside chronic liver disease or cirrhosis.[3] Consequently, hepatic insufficiency is typically present in various degrees at the time of cancer diagnosis. Compared with the management and prognosis of other solid tumors, those of HCC rely heavily on tumor burden and functional hepatic reserve.[4]

The Barcelona Clinic Liver Cancer (BCLC) system is widely used for HCC prediction and therapeutic selection.[5] Intermediate-stage HCC is heterogeneous in terms of tumor size (<3–>10 cm), number (a large solitary tumor [>5 cm] to numerous small tumors), and effects on liver function (Child–Pugh score: 5–9). According to the BCLC guidelines, transarterial chemoembolization (TACE) is the only recommended option for patients with intermediate-stage HCC.[6] However, hepatic resection has been demonstrated to provide survival benefits in selected patients with BCLC stage B HCC.[7–9]

Various noninvasive models have been proposed to assess functional hepatic reserve or fibrosis severity.[10] The Child–Pugh classification has been widely used for decades to evaluate liver decompensation severity.[11] The model for end-stage liver disease is used to assess survival in patients with end-stage liver disease.[12] The albumin–bilirubin (ALBI) grade, based on serum albumin and total bilirubin level,[13] and platelet–albumin–bilirubin (PALBI) grade, which additionally includes platelet count,[14] are useful markers of hepatic reserve in patients with HCC. ALBI-based models and the ALBI score can be used to predict overall survival (OS) in patients undergoing surgical resection,[15,16] radiofrequency ablation (RFA),[15,17,18] TACE,[19,20] and radioembolization.[21] Moreover, noninvasive indices, including FIB-4 and the aspartate aminotransferase (AST)-to-platelet ratio, can be used to assess liver fibrosis severity.[22,23] In addition, other models, including the Lok index,[24] cirrhosis discriminant index (CDS),[25] Göteborg University Cirrhosis Index (GUCI),[26] and King score,[27] have also been used to predict the presence of advanced fibrosis or cirrhosis. However, few studies have investigated the performance of these noninvasive models in predicting OS among patients with intermediate-stage HCC.[19] In this retrospective study, we assessed the feasibility and compared the prognostic role of these 10 functional hepatic reserve or fibrosis models.

2. Methods

2.1. Patients

This retrospective study included 612 consecutive patients with intermediate-stage HCC from January 2012 to November 2018 at China Medical University Hospital. RFA for treating intermediate-stage HCC is an emerging field,[28] and only 19 of 612 patients received RFA. Therefore, patients undergoing RFA were excluded. Patients who received liver transplantation (n = 13), systemic therapy (n = 5), radiotherapy (n = 5), or hospice care and those who were transferred to other hospitals (n = 77) were also excluded. Finally, 493 patients were included in the analysis (Fig. 1).

Demographic and biochemical data, complete blood count, presence of viral hepatitis features, presence of diabetes mellitus, and performance status were recorded at baseline. Tumor assessment was performed using contrast-enhanced dynamic computed tomography (CT) or magnetic resonance imaging (MRI).

2.2. Diagnosis and laboratory tests

HCC was diagnosed on the basis of histology or typical radiological presentations in at least two imaging modalities, including abdominal ultrasonography, contrast-enhanced dynamic CT, MRI, and hepatic arterial angiography.[29,30] Performance status was evaluated according to the Eastern Cooperative Oncology Group performance scale.[31] Complete blood count analyses (Sysmex HST series, Sysmex, Kanagawa, Japan) and blood biochemistry tests (Beckman Coulter, Brea, CA) were performed in the central laboratory of the hospital. Patients were considered to have hepatitis B virus (HBV) infection if serum HBsAg was detected. Hepatitis C virus (HCV) infection was defined as the presence of serum anti-HCV antibody for >6 months and detectable HCV RNA (detection limit = 15 IU/mL; COBAS

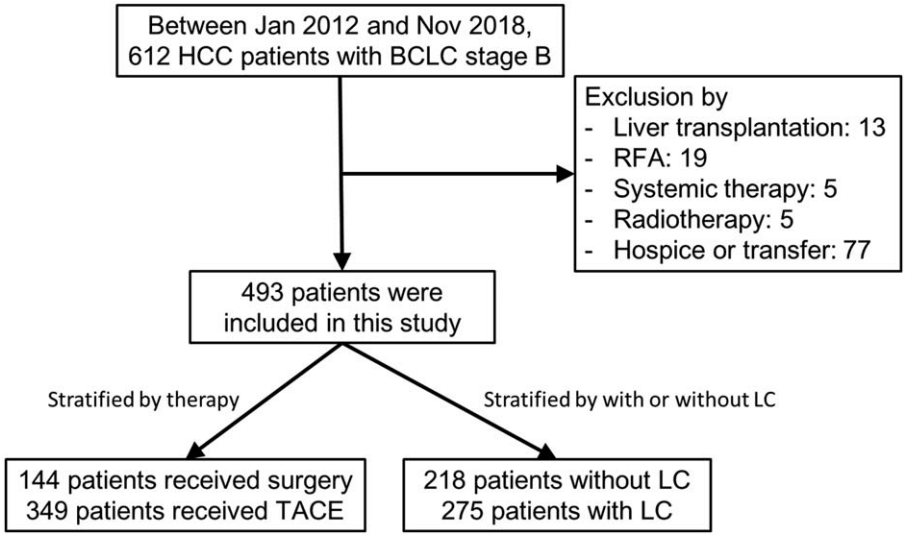

Figure 1. Flow chart of patient enrolment and stratification in this study.

Ampliprep/COBAS TaqMan HCV test [Roche Diagnostics, Branchburg, NJJ]). Liver cirrhosis (LC) was diagnosed through unequivocal clinical, ultrasonographic, or pathological analysis.

2.3. Calculation of 10 liver functional reserve or fibrosis models

The formulas for 10 noninvasive assessments, including Child–Pugh score,[11] model for end-stage liver disease score,[12] CDS,[25] AST-to-platelet ratio,[23] FIB-4,[22] Lok index,[24] GUCI score,[26] King score,[27] ALBI grade,[13] and PALBI grade,[14] are listed in Supplementary Table 1, http://links.lww.com/MD/G371. The calculation was based on clinical variables and serum biochemistries obtained at the time of diagnosis.

2.4. Treatment

The medical records of patients with HCC were reviewed by the multidisciplinary liver cancer team at China Medical University Hospital. The therapeutic decision was made according to the hospital's Liver Cancer Clinical Practice Guidelines, which are based on the guidelines by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver.[29,30] The indication and extent of partial hepatectomy were determined by experienced surgeons in our hospital, as described previously.[32] TACE was indicated in the case of Child–Pugh class A or B and patent main portal vein or main portal vein thrombosis with cavernous transformation. Its procedure is described in detail elsewhere.[33]

2.5. Ethics statement

This study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Research Ethics Committee of China Medical University Hospital, Taichung, Taiwan (CMUH108-REC3-140). Each patient's identification number was encrypted for privacy protection; thus, the need for informed consent was waived.

2.6. Statistical analyses

Continuous variables are presented as the median (interquartile range), and categorical variables are presented as a frequency (percentage). The data were censored in case of death, in case of loss to follow-up, or at the end of follow-up (June 30, 2020), whichever occurred first. Between-group comparisons of continuous variables were performed using the Mann–Whitney *U* test. Variables with $P < .10$ in the univariate analysis were subjected to multivariate Cox regression analysis to determine their associations with OS. The survival prediction performance of the noninvasive models was compared using receiver operating characteristic (ROC) curve analysis with the DeLong test.[34] Kaplan–Meier analysis with the log-rank test was used to compare the OS among patient subgroups. All statistical analyses were performed using SPSS (version 25.0, IBM, New York). A 2-sided *P* value of $<.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Of the 493 patients, 373 (75.7%) were male and 275 (55.8%) had LC. Among all patients, 114 (23.1%), 254 (51.5%), 197 (40.0%), and 153 (31.0%) patients reported drinking alcohol, having HBV infection, having HCV infection, and having diabetes mellitus, respectively. The median age of the patients was 64 (55–72) years. Most patients had a tumor volume of ≤50% of the liver volume (n = 424, 86.0%), and the maximum tumor size was 6.0 (4.0–8.5) cm. The median follow-up period was 26.07 (9.77–48.27) months. The median α-fetoprotein (AFP) level was 36.25 (6.13–552.91) ng/mL. The median Cancer of the Liver Italian Program (CLIP) score was 1 (1–2). The 10 models are presented in Table 1. In all, 144 (29.2%) and 349 (70.8%) patients underwent surgery and TACE, respectively. Patients with LC had higher AST, alanine aminotransferase (ALT), and total bilirubin levels; higher international normalized ratios (INRs); lower platelet counts; lower albumin levels; and shorter OS (29.87 vs 43.87 months, $P = .003$) than those without LC. Patients with LC also had higher scores or grades in all models (Table 1).

3.2. Prognostic performance of the 10 functional hepatic reserve or fibrosis models

Among the 10 models, the ALBI score had the highest area under the ROC curve (AUROC) value (0.644 [95% confidence interval, CI: 0.595–0.693]) in all patients. In the subgroup analysis, Lok index, PALBI score, ALBI score, and Lok index had the highest AUROC values among patients without cirrhosis (n = 218), patients with cirrhosis (n = 275), patients undergoing TACE (n = 349), and patients undergoing surgery (n = 144), respectively (Table 2).

3.3. ALBI grade, PALBI grade, and Lok index grade as predictors of OS in all patients, patients undergoing TACE, and patients undergoing surgery

We investigated the survival prediction ability of the models. Univariate Cox regression analysis identified age, LC, AST (≤40 U/L), AFP (<400 ng/mL), tumor volume (≤50% of liver volume), surgery, and ALBI grade 1 as significantly associated factors. In the multivariate Cox regression analysis, younger age (hazard ratio [HR]: 0.984, 95% CI: 0.974–0.995, $P = .003$), AST (≤40 U/L, HR: 1.954, 95% CI: 1.402–2.722, $P < .001$), AFP (<400 ng/mL, HR: 2.007, 95% CI: 1.547–2.604, $P < .001$), tumor volume (≤50% of liver volume, HR: 2.043, 95% CI: 1.472–2.835, $P < .001$), surgery (HR: 1.888, 95% CI: 1.345–2.652, $P < .001$), and ALBI grade 1 (HR: 1.597, 95% CI: 1.222–2.086, $P = .001$) were independent predictors of longer OS in all patients (Table 3). Moreover, Lok index grade 1, ALBI grade 1, and Lok index grade 1 were independent predictors of longer OS in patients without LC (Supplemental Table 2, http://links.lww.com/MD/G372), those undergoing TACE (Supplemental Table 3, http://links.lww.com/MD/G373), and those undergoing surgery (Supplemental Table 4, http://links.lww.com/MD/G374), respectively. In patients with LC, PALBI grade 1 was not an independent predictor of OS; however, platelet count, AFP (<400 ng/mL), tumor volume (≤50%), and ALBI grade 1 were independent predictors of longer OS in patients with LC (Supplemental Table 5, http://links.lww.com/MD/G375).

Patients undergoing surgery had longer OS compared with those undergoing TACE (Fig. 2A). Significant differences in OS were observed for different ALBI grades (1 vs 2–3) in all patients (Fig. 2B), patients with LC (Fig. 2D), and patients undergoing TACE (Fig. 2E) and for different Lok index grades (1 vs 2–3) in

Table 1

Patient demographics, baseline characteristics, and therapeutic response.

Variables	Total (n = 493)	Noncirrhosis (n = 218)	Cirrhosis (n = 275)	P*
Age, y	64 (55–72)	64 (53–73)	65 (57–72)	.370
Sex (male), *n* (%)	373 (75.7)	172 (78.9)	201 (73.1)	.136
Platelet count ($\times 10^9$/L)	160 (112–225)	190 (141–250)	136 (92–193)	<.001
AST, U/L	53 (37–86)	47 (33–75)	61 (42–95)	<.001
ALT, U/L	46 (30–69)	42 (28–60)	50 (31–76)	.002
Total bilirubin, mg/dL	0.9 (0.6–1.2)	0.7 (0.6–1.1)	1.0 (0.7–1.3)	<.001
Albumin, g/dL	4.0 (3.5–4.4)	4.1 (3.7–4.5)	3.9 (3.4–4.2)	<.001
INR	1.07 (1.02–1.14)	1.06 (1.01–1.11)	1.09 (1.03–1.16)	<.001
Creatinine, mg/dL	0.93 (0.77–1.12)	0.96 (0.79–1.11)	0.90 (0.75–1.12)	.142
Etiology				
Alcohol	114 (23.1)	43 (19.7)	71 (25.8)	.111
HBV	254 (51.5)	130 (59.6)	124 (45.1)	.002
HCV	197 (40.0)	67 (30.7)	130 (47.3)	<.001
Diabetes mellitus	153 (31.0)	62 (28.4)	91 (33.1)	.268
Child-Pugh score	5 (5–6)	5 (5–5)	5 (5–6)	<.001
Class A/B	424/68 (86.2/13.8)	198/19 (91.2/8.8)	226/49 (82.2/17.8)	.004
MELD score	8 (7–10)	8 (7–9)	8 (7–11)	<.001
CDS	6 (4–7)	5 (4–6)	6 (5–7)	<.001
APRI	0.99 (0.62–2.10)	0.73 (0.47–1.24)	1.40 (0.74–2.85)	<.001
FIB-4	3.21 (1.98–5.87)	2.64 (1.46–3.89)	4.31 (2.53–7.36)	<.001
Lok index	0.55 (0.38–0.75)	0.46 (0.29–0.64)	0.63 (0.47–0.82)	<.001
Lok index grade 1/2/3	203/194/94 (41.3/39.5/19.1)	125/72/20 (57.6/33.2/9.2)	78/122/74 (28.5/44.5/27.0)	<.001
GUCI score	1.07 (0.64–2.33)	0.79 (0.50–1.35)	1.49 (0.85–3.25)	<.001
King score	23.90 (13.05–53.15)	17.10 (9.87–28.66)	33.68 (16.61–69.64)	<.001
ALBI grade 1/2/3	253/211/24 (51.8/43.2/4.9)	138/72/8 (63.3/33.0/3.7)	115/139/16 (42.6/51.5/5.9)	<.001
PALBI grade 1/2/3	219/186/83 (44.9/38.1/17.0)	113/72/33 (51.8/33.0/15.1)	106/114/50 (39.3/42.2/18.5)	.011
AFP, ng/mL	36.25 (6.13–552.91)	27.56 (4.93–405.94)	48.79 (7.54–701.47)	.021
AFP ≥400 ng/mL	137 (27.8)	54 (24.8)	83 (30.2)	.204
Max. tumor size, cm	6.0 (4.0–8.5)	6.7 (5.0–9.4)	5.5 (3.5–7.6)	<.001
Tumor volume ≤50%/>50%	424/69 (86.0/14.0)	186/32 (85.3/14.7)	238/37 (86.5/13.5)	.697
CLIP score	1 (1–2)	1 (0–2)	1 (1–2)	<.001
Therapy				<.001
Surgery	144 (29.2)	112 (51.4)	32 (11.6)	
TACE	349 (70.8)	106 (48.6)	243 (88.4)	
Overall survival, mo	34.70 (95% CI 28.09–41.31)	43.87 (95% CI 20.22–67.52)	29.87 (95% CI 23.35–36.39)	.003

Data are presented as a number (percentage) or the median (interquartile range) unless otherwise indicated.

AFP = α-fetoprotein, ALBI = albumin–bilirubin, ALT = alanine aminotransferase, APRI = AST-to-platelet ratio index, AST = aspartate aminotransferase, CDS = cirrhosis discriminant score, CI = confidence interval, CLIP = Cancer of the Liver Italian Program, GUCI = Göteborg University Cirrhosis Index, HBV = hepatitis B virus, HCV = hepatitis C virus, INR = international normalized ratio, IQR = interquartile range, MELD = model for end-stage liver disease, PALBI = platelet–albumin–bilirubin, TACE = transarterial chemoembolization.

* All comparisons, except overall survival, were performed using the Mann–Whitney *U* test between patients with and without liver cirrhosis. The comparison of overall survival was performed using Kaplan–Meier analysis with the log-rank test between patients with and without liver cirrhosis.

Table 2

Comparison of the prognostic performance of noninvasive indexes for patients with BCLC stage B hepatocellular carcinoma according to receiver-operating character curve analysis with the DeLong test.

Predictors	Overall (n = 493)	Noncirrhosis (n = 218)	Cirrhosis (n = 275)	TACE (n = 349)	Surgery (n = 144)
Child-Pugh score	0.601 (0.551–0.651)*	0.595 (0.519–0.671)†	0.584 (0.515–0.653)	0.582 (0.521–0.644)	0.572 (0.475–0.669)
MELD	0.583 (0.532–0.634)*	0.566 (0.489–0.643)†	0.578 (0.508–0.648)	0.561 (0.499–0.624)	0.563 (0.465–0.660)
CDS	0.582 (0.531–0.633)*	0.629 (0.555–0.703)†	0.520 (0.451–0.590)*	0.538 (0.476–0.601)*	0.594 (0.500–0.687)
APRI	0.604 (0.554–0.655)	0.661 (0.587–0.734)	0.536 (0.466–0.607)	0.572 (0.509–0.635)	0.585 (0.490–0.679)
FIB-4	0.632 (0.582–0.682)	0.683 (0.612–0.754)	0.574 (0.504–0.643)	0.608 (0.547–0.670)	0.589 (0.469–0.683)
Lok index	0.624 (0.574–0.674)	0.684 (0.612–0.755)	0.552 (0.482–0.622)	0.583 (0.521–0.645)	0.646 (0.553–0.739)
GUCI score	0.606 (0.555–0.657)	0.662 (0.589–0.735)	0.536 (0.465–0.606)	0.571 (0.507–0.634)	0.589 (0.494–0.683)
King score	0.619 (0.569–0.670)	0.667 (0.595–0.739)	0.559 (0.489–0.629)	0.595 (0.532–0.657)	0.578 (0.483–0.672)
ALBI	0.644 (0.595–0.693)	0.669 (0.597–0.741)	0.598 (0.529–0.668)	0.625 (0.564–0.686)	0.579 (0.484–0.674)
PALBI	0.620 (0.570–0.670)	0.624 (0.550–0.698)	0.603 (0.533–0.672)	0.611 (0.549–0.672)	0.581 (0.485–0.676)

Data are presented as the mean (95% confidence interval).

ALBI = albumin–bilirubin, APRI = aspartate transaminase-to-platelet ratio index, CDS = cirrhosis discriminant score, GUCI = Göteborg University Cirrhosis Index, MELD = model for end-stage liver disease, PALBI = platelet–albumin–bilirubin.

* $P < .05$ compared with the ALBI score in the same subgroup.

† $P < .05$ compared with the Lok score in the same subgroup.

Table 3

Factors associated with overall survival in all patients (n = 493).

Character		Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age, y		0.981 (0.971–0.991)	<.001	0.984 (0.974–0.995)	.003
Sex	Female vs male	0.948 (0.722–1.245)	.701		
Alcohol	Yes vs no	0.952 (0.712–1.271)	.737		
HBV	Yes vs no	1.245 (0.978–1.585)	.076		
HCV	Yes vs no	0.794 (0.623–1.011)	.061		
Diabetes mellitus	Yes vs no	0.895 (0.695–1.152)	.389		
Liver cirrhosis	Yes vs no	0.690 (0.540–0.881)	.003		
Platelet ($\times 10^9$/L)		1.000 (0.998–1.001)	.534		
AST, U/L	≤40 vs >40	2.516 (1.871–3.384)	<.001	1.954 (1.402–2.722)	<.001
ALT, U/L	≤40 vs >40	1.117 (0.878–1.422)	.367		
Creatinine, mg/dL		0.959 (0.873–1.053)	.374		
AFP, ng/mL	<400 vs ≥400	1.898 (1.475–2.442)	<.001	2.007 (1.547–2.604)	<.001
Tumor volume	≤50% vs >50%	2.320 (1.708–3.152)	<.001	2.043 (1.472–2.835)	<.001
Therapy	Surgery vs TACE	2.288 (1.710–3.061)	<.001	1.888 (1.345–2.652)	<.001
ALBI grade	1 vs 2–3	2.224 (1.741–2.840)	<.001	1.597 (1.222–2.086)	.001

AFP = α-fetoprotein, ALBI = albumin–bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, HBV = hepatitis B virus, HCV = hepatitis C virus, HR = hazard ratio, TACE = transarterial chemoembolization.

patients without LC (Fig. 2C) and patients undergoing surgery (Fig. 2F).

4. Discussion

Patients with intermediate-stage HCC have heterogeneous tumor burden and liver function; therefore, the clinical benefits of TACE and surgical resection vary considerably in this patient group.[7,35] A good noninvasive model thus plays an essential role in therapeutic decision-making and prognostic prediction in these patients. Our findings demonstrate that among the 10 models analyzed, ALBI grade best predicts OS in all patients, patients with cirrhosis, and patients undergoing TACE and Lok index grade best predicts OS in patients without cirrhosis and those undergoing surgery.

Although noninvasive models are currently used as predictive tools in patients with HCC undergoing surgery, RFA, TACE, and radioembolization,[15–21] few studies have compared the survival prediction performance of the noninvasive models in intermediate-stage HCC. In this study, we enrolled a medium-sized, well-characterized, and adequately followed-up intermediate-stage HCC cohort. Our results revealed that 275 patients with LC (of the 493 patients in this study [55.8%]) had higher AST, ALT, and total bilirubin levels; higher INRs; lower platelet counts; lower albumin levels; and a shorter OS. Moreover, all patients with LC had higher scores/grades than those without LC in all the models. For different treatment modalities, Yin et al revealed that patients with intermediate-stage HCC treated with surgical resection had a median survival duration of 41 months, which was longer than those treated with TACE (14 months).[36] Similarly, our study results indicate that patients undergoing surgery had longer OS (61.2 months, 95% CI: 55.2–67.1) than those undergoing TACE (38.1 months, 95% CI: 34.2–42.0, $P < .001$).

Among the 10 noninvasive models, the ALBI score had the highest AUROC value in all patients. The ALBI score and ALBI-based models have high accuracy in assessing functional hepatic reserve and prognosis in patients with HCC undergoing surgical resection, RFA, TACE, and radioembolization.[15–21] Our study results also revealed that patients with intermediate-stage HCC and ALBI grade 1 consistently had higher OS compared with those with ALBI grade 2–3 (HR: 1.597, 95% CI: 1.222–2.086, $P = .001$). In addition to ALBI grade 1, younger age, lower AST level (≤40 U/L), lower AFP level (<400 ng/mL), lower tumor volume (≤50%), and surgery were independent predictors of longer OS in all patients. These findings suggest that functional hepatic reserve and tumor status are the main determinants of survival. ALBI grade serves as an accurate prognostic model for patients undergoing surgical resection.[15,16] However, our data indicate that Lok index grade 1 has the highest predictive performance for OS in patients with intermediate-stage HCC undergoing surgical resection. This difference may have resulted from differences in the characteristics of the enrolled patients. However, BCLC remains the standard guideline for managing patients with HCC, and subgroup stratification may be more appropriate for OS prediction in this BCLC stage.

Although the PALBI score had the highest AUROC value for predicting OS in patients with cirrhosis, PALBI grade 1 was not an independent predictor of OS in the multivariate Cox regression analysis. However, its components (platelet count and ALBI grade 1) as well as AFP (<400 ng/mL) and tumor volume (≤50%) were independent predictors of OS in patients with LC (Supplemental Table 5, http://links.lww.com/MD/G375).

This study had several limitations. First, we included only patients with intermediate-stage HCC; therefore, caution should be exercised during extrapolation of our findings to other BCLC stages. Second, this was a single-center study, and most patients had HBV infection (51.5%); therefore, external validation in other regions is required. Third, because this study was conducted on patients at a referral medical center in central Taiwan, referral bias could not be entirely avoided.

In conclusion, our results reveal that among the 10 noninvasive models evaluated, ALBI grade had the highest OS prediction performance in all patients with intermediate-stage HCC, those with LC, and those undergoing TACE and Lok grade was the best model for predicting OS in patients with intermediate-stage HCC without LC and in those undergoing surgery. These results may help guide clinical decision-making for patients with intermediate-stage HCC who wish to receive different treatment options.

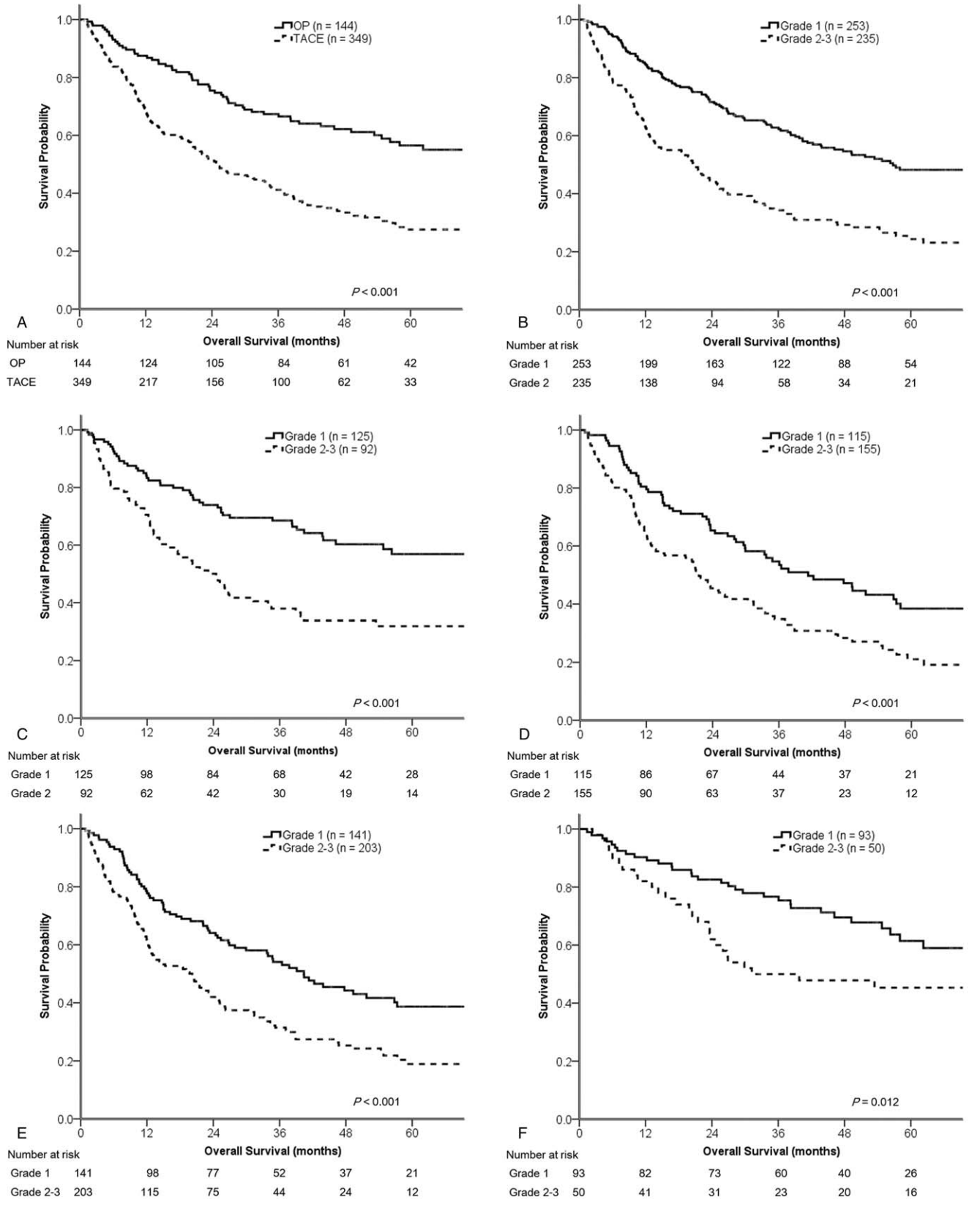

Figure 2. Kaplan–Meier analyses of overall survival. (A) Patients undergoing surgery (OP) vs. transarterial chemoembolization (TACE). (B) All patients: albumin–bilirubin (ALBI) grade 1 vs grade 2–3. (C) Patients without liver cirrhosis: Lok grade 1 vs. grade 2–3. (D) Patients with liver cirrhosis: ALBI grade 1 vs grade 2–3 (E) Patients undergoing TACE: ALBI grade 1 vs grade 2–3. (F) Patients undergoing surgery: Lok index grade 1 vs grade 2–3.

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