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ORIGINAL ARTICLE

The indocyanine green retention test as a noninvasive marker for esophageal varices in patients with hepatocellular carcinoma

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Abstract

Background: The indocyanine green 15-minute retention (ICG-r15) test was considered as a noninvasive marker of esophageal varices (EV) in cirrhotic patients. However, the performance of ICG-r15 in patients with hepatocellular carcinoma (HCC) has rarely been assessed. The aim of this study is to evaluate the value of ICG-r15 as a noninvasive marker of EV in patients with HCC.

Methods: From October 2007 to December 2018, the study retrospectively enrolled 137 HCC patients with compensated hepatic function who received ICG-r15 tests and endoscopy screening for EV. The predictive value of the ICG-r15 test and other noninvasive markers was also evaluated for the diagnosis of EV, including the aspartate aminotransferase (AST)/alanine aminotransferase ratio, platelet count/spleen diameter ratio, AST/platelet ratio index, Lok index, FIB-4, and Park index.

Results: In the study cohort, 30 (21.9%) patients had EV. The area under the receiver operating characteristic curve for determining EV by ICG-r15 was 0.784 (95% CI: 0.686–0.881, −2 ln (L): 77.889, Akaike information criterion: 79.889), and it had the best predictive value compared with other noninvasive markers. The cutoff value of ICG-r15 to identify EV was 31.0%, and it had 40.0% sensitivity and 98.1% specificity. The cutoff value to exclude EV was 9.5% with 86.7% sensitivity and 50.5% specificity. In the multivariate analysis, ICG-r15 (odds ratio [OR]: 1.062, 1.014–1.114; $p = 0.015$) and the Park index (OR: 1.535, 1.091–2.159; $p = 0.014$) were independently related to the presence of EV.

Conclusion: ICG-r15 is a practical noninvasive marker with cutoff values of 9.5% for excluding EV and 31.0% for identifying EV in patients with HCC.

Keywords: Esophageal varices; Hepatocellular carcinoma; Indocyanine green retention test; Noninvasive markers; Primary prevention

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the major causes of mortality worldwide, and the incidence has been increasing in the past few years.[1] The presence of esophageal varices (EV) is a negative prognostic factor for patients with HCC.[2,3] Esophagogastroduodenoscopy (EGD) is currently the standard tool for screening EV. The Baveno V consensus suggests endoscopic screening for EV among all cirrhotic patients during diagnosis.[4] However, this approach is limited by its cost and invasiveness. Therefore, it is necessary to develop noninvasive markers, and several noninvasive markers have been proposed.[5–14] A combination of platelet counts and liver stiffness measurements by transient elastography can be used to select cirrhotic patients who may not require endoscopic screening for EV.[15] However, the usefulness of transient elastography for patients with HCC remains in doubt.[16]

Indocyanine green (ICG) is a water-soluble tricarbocyanine dye that is injected intravenously and mainly binds to albumin and alpha-1 lipoproteins. It is almost exclusively extracted by the hepatic parenchyma and rapidly excreted into the bile without undergoing biotransformation and with no enterohepatic circulation.[17–19] ICG clearance is a quantitative test for liver parenchymal function and hepatic blood flow.[20]

The ICG retention test has become a safe, reproducible, and noninvasive tool for the assessment of liver function. It is not only used for preoperation survey for hepatic surgery[21,22] but also as a prognostic marker in patients with liver cirrhosis.[23,24] A previous study demonstrated that the ICG 15-minute retention (ICG-r15) test has good correlation with the hepatic venous pressure gradient (HVPG).[25] The results also showed that ICG-r15 < 10% can be used to rule out the presence of EV, whereas ICG-15 ≥ 22.9% can be used as an indicator of EV in cirrhotic patients.

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Organic anion transporting polypeptides involving ICG transportation are different between patients with HCC and those who are cirrhotics.[26,27] However, patients with HCC and concomitant EV still have significantly higher ICG-r15 levels than those who do not have EV.[28] Patients with resectable HCC and clinically significant portal hypertension (HVPG ≥ 10 mmHg) also have more EV than those who do not have clinically significant portal hypertension (44.1% vs 11.1%).[29] Therefore, we hypothesized that the ICG-r15 test could be a useful noninvasive predictor of EV in patients with HCC. The aim of our study is to clarify the usefulness of ICG-r15 and to compare it with other noninvasive markers for predicting EV in compensated patients with HCC.

2. METHODS

2.1. Patients

This study is a retrospective study with prospective collection of data. The study enrolled 6,495 patients with newly diagnosed HCC who fulfilled the diagnostic criteria of the American Association for the Study of Liver Disease (AASLD) according to the cancer registration system at a single tertiary center from October 2007 to December 2018. The baseline characteristics were prospectively recorded, including sex, age, biochemistry data, cause of HCC, Child–Turcotte–Pugh score, Barcelona Clinic Liver Cancer (BCLC) stage, status of portal vein thrombosis, HCC treatment, and mortality.

The exclusion criteria of the study were as follows: (1) patients who did not have an ICG-r15 test at the time of HCC diagnosis, (2) patients who did not receive endoscopic screening for EV at the time of HCC diagnosis, (3) patients with decompensated liver disease, and (4) patients who were diagnosed with portal vein thrombosis or invasion. Compensated patients with HCC were defined as those with an absence of ascites, variceal hemorrhage, hepatic encephalopathy, or jaundice and a CTP score of 5 or 6. The diameter of the spleen was measured on abdominal CT scans or MRI if CT scans was not available. The study was performed in accordance with the Declaration of Helsinki and current ethical guidelines. It was also approved by the Institutional Review Board.

2.2. ICG retention test

Indocyanine green (Daiichi Sankyo Propharma Co., LTD., Osaka, Japan) was injected intravenously at a dose of 0.5 mg/kg of body weight after a basal blood sampling on the opposite arm. A blood sample was then collected every 5 minutes for 15 minutes. The ICG absorbance in plasma was measured at 800 nm using an AU680 Clinical Chemistry Analyzer (Beckman Coulter, Inc., CA).

2.3. Noninvasive markers for prediction of EV

The AAST/ALT ratio (AAR),[6] Albumin–Bilirubin grade (ALBI),[30] ALBI grade and platelet count (ALBI-PLT score),[31] platelet count/spleen diameter ratio (PSDR),[5] AST/platelet ratio index (APRI),[8] Lok index,[9] FIB-4,[10] and Park index[11] were calculated according to published equations for all patients.

2.4. Endoscopic evaluation

The size of the EV was recorded in accordance with the criteria proposed by Beppu et al:[32] small and straight varices were recorded as F_1, moderately sized and tortuous varices were recorded as F_2, and large and tumorous varices were recorded as F_3.

2.5. Statistical analysis

Fisher's exact test or a chi-squared test with Yates' correction was performed to compare the categorical variables, and a student's *t* test was used to compare continuous variables. The diagnostic accuracy of the model was assessed by analyzing the receiver operating characteristic (ROC) curve. The cutoff value for indicating the presence of EV was collected using the highest positive likelihood ratio (LR^+), and the lowest negative likelihood ratio (LR^-) was used as a cutoff value for ruling out EV.

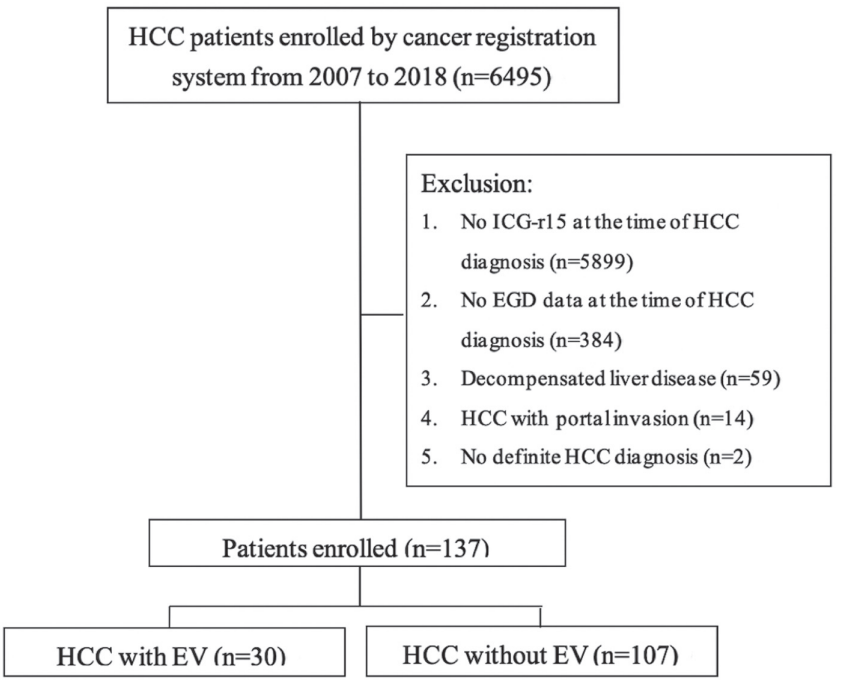

Fig. 1. Flow chart of the study. EGD = esophagogastroduodenoscopy; EV = esophageal varices; HCC = hepatocellular carcinoma; ICG-r15 = indocyanine green 15-minute retention test.

The relative goodness of every model was determined using the Akaike information criterion, AIC = – 2 ln(L) + 2k, where L is the maximized value of the likelihood function for the estimated logistic regression model and k is the number of parameters.[33] Variables that had statistical significance ($p < 0.05$) or near statistical significance ($p < 0.1$) in the univariate analysis were subjected to a multivariate analysis via a backward stepwise Cox regression model. p values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NYs).

3. RESULTS

3.1. Baseline clinical characteristics

A flow chart of the study is shown in Fig. 1 and Table 1 shows the demographic characteristics of the study population. A total of 137 HCC patients with compensated liver function were enrolled. Among the whole study population, 30 patients had EV (21.9%), and of those, 1 patient had small varices (F_1) with red color sign, 14 patients had small varices (F_1) without red color sign, and 15 patients had medium or large varices (F_2 or F_3).

Table 1.

Baseline characteristics of patients

Baseline characteristics	Total (n = 137)	EV (n = 30)	No EV (n = 107)	*p*
Age, median (range), years	66 (58–73)	62 (57–74)	66 (59–73)	0.849
Sex (male), n (%)	102 (74.5)	24 (80.0)	78 (72.9)	0.431
Etiology, n (%)				
HBV	54 (39.4)	12 (40.0)	42 (39.3)	0.941
HCV	38 (27.7)	9 (30.0)	29 (27.1)	0.754
HBV + HCV	2 (1.5)	0 (0)	2 (1.9)	0.451
Alcohol	5 (3.6)	0 (0)	5 (4.7)	0.228
Alcohol + HBV	11 (8.0)	3 (10.0)	8 (7.5)	0.653
Alcohol + HCV	3 (2.2)	1 (3.3)	2 (1.9)	0.628
Others	24 (17.5)	5 (16.7)	19 (17.8)	0.890
MELD score	7.67 (6.98–8.72)	8.27 (7.60–8.91)	7.46 (6.79–8.72)	0.286
Spleen diameter, cm	9.7 (8.8–10.9)	10.5 (9.6–12.6)	9.5 (8.7–10.7)	0.008
Serum lab data				
ICG-r15, %	12 (8–18)	22 (13–40)	10 (7–16)	<0.001
Prothrombin time, INR	1.06 (1.01–1.11)	1.11 (1.05–1.17)	1.06 (1.00–1.10)	<0.001
Platelet count, K/cumm	134 (96–185)	88 (67–152)	146 (120–198)	0.007
Creatinine, mg/dL	0.93 (0.79–1.06)	0.84 (0.78–1.04)	0.94 (0.79–1.10)	0.259
ALT, U/L	38 (25–76)	45 (31–93)	37 (24–65)	0.111
AST, U/L	36 (25–71)	57 (35–108)	39 (27–70)	0.034
Albumin, g/dL	4.1 (3.8–4.4)	3.8 (3.4–4.1)	4.0 (3.6–4.4)	0.092
Total bilirubin, mg/dL	0.72 (0.53–0.97)	1.00 (0.70–1.16)	0.64 (0.48–0.84)	<0.001
Tumor factors				
Tumor size, cm	3.0 (2.0–5.0)	2.3 (1.5–4.7)	3.3 (2.1–6.6)	0.006
Single tumor, %	103 (75.2)	24 (80.0)	79 (73.8)	0.489
AFP, ng/ml	17.0 (6.0–166.0)	49.9 (8.6–823.0)	15.0 (5.1–122.7)	0.632
Tumor staging and treatment modality				
BCLC stage (0/A/B/C/D) (%)	4/64/61/7/1 (2.9/46.7/44.5/5.1/0.7)	1/15/11/3/0 (3.3/50.0/36.7/10.0/0)	3/49/50/4/1 (2.8/45.8/46.7/3.7/0.9)	0.605
Treatment modality (resection surgery/RFA/TACE/Others)[a] (%)	83/15/22/17 (60.6/10.9/16.1/12.4)	9/7/9/5 (30.0/23.3/30.0/16.7)	74/8/13/12 (69.2/7.5/12.1/11.2)	0.001
Treatment modality (curative/ noncurative) (%)	105/32 (76.6/23.4)	17/13 (56.7/43.3)	88/19 (82.2/17.8)	0.003
Noninvasive models				
AAR	1.07 (0.82–1.38)	1.14 (0.86–1.40)	1.07 (0.80–1.36)	0.837
APRI	0.61 (0.38–1.45)	1.34 (0.70–2.47)	0.53 (0.35–1.00)	0.013
Park index	-1.10 (-2.14 to -0.53)	0.38 (-1.29 to 1.49)	-1.34 (-2.28 to -0.48)	<0.001
PSDR	1529.1 (1012.5–2250.6)	885.8 (579.4–1350.1)	1618.4 (1220.0–2329.6)	0.005
Lok index	0.50 (0.35–0.71)	0.68 (0.54–0.81)	0.48 (0.33–0.64)	<0.001
FIB-4	2.76 (1.97–5.86)	6.53 (3.68–8.23)	2.58 (1.79–4.45)	<0.001
ALBI grade				0.010
Grade 1	59 (43.1)	6 (20.0)	53 (49.5)	
Grade 2	53 (56.2)	0 (0)	53 (49.5)	
Grade 3	1 (0.7)	0 (0)	1 (0.9)	
ALBI–PLT score				0.007
=2	35 (25.5)	2 (6.7)	33 (30.8)	
>2	102 (74.5)	28 (93.3)	74 (69.2)	

AAR = AST/ALT ratio; ALBI grade = albumin-bilirubin grade; ALBI-PLT score = albumin-bilirubin grade and platelet count; AFP = alpha-fetoprotein; ALT = alanine transaminase; AST = aspartate transaminase; APRI = AST/platelet ratio index; BCLC stage = Barcelona clinic liver cancer stage; HBV = hepatitis B virus; HCV = hepatitis C virus; ICG-r15 = indocyanine green 15-minute retention test; PAI= Percutaneous acetic acid injection; PSDR = platelet count/spleen diameter ratio; RFA= Radiofrequency ablation; TACE= Transcatheter arterial chemoembolization.

[a]Other treatments of total population including six patients received TACE before resection surgery, one patient received PAI, one patient received Yttrium-90, two patients received supportive care, three patients refused treatment, three patients received radiotherapy, and three patients received target therapy.

3.2. Factors associated with the presence of EV

Compared with patients without EV, those who did have EV had a larger spleen, a longer prothrombin time, lower platelet counts, higher serum aspartate aminotransferase (AST), and higher total bilirubin levels. Regarding tumor factors, patients with EV had smaller tumor size but lower rates of receiving curative treatment for HCC. Among the noninvasive markers, ALBI grade, ALBI–PLT score, APRI, the Park index, PSDR, the Lok index, FIB-4, and ICG-r15 were significantly associated with the presence of EV, but not AAR. In the multivariate analysis, ICG-r15 (odds ratio [OR]: 1.062, 1.014–1.114; $p = 0.015$) and the Park index (OR: 1.535, 1.091–2.159; $p = 0.014$) were independently related to the presence of EV.

3.3. Performance of noninvasive markers for the diagnosis of EV

Table 2 shows the diagnostic performance of noninvasive markers for the presence of EV. ICG-r15 demonstrated the largest area under the ROC curve (AUROC: 0.784, 95% CI: 0.686–0.881) and the lowest AIC values (AIC: 79.889, −2 ln (L): 77.889), which suggest that ICG-r15 is the best tool for the diagnosis of EV. For medium-to-large EV and high-risk EV, the ICG-r15 also showed good value for diagnosis and the AUROC were 0.777 (95% CI:0.661–0.892) and 0.746 (95% CI: 0.622–0.869), respectively.

3.4. ICG-r15 cutoff values for the diagnosis of EV

The use of ICG-r15 < 9.5% for the exclusion of EV had a sensitivity of 86.7% (LR^- = 0.269), and the use of ICG-r15 ≥ 31.0% for the diagnosis of EV showed a specificity of 98.1% (LR^+ = 21.05) (Table 3). When focusing on medium to large EV, ICG-r15 < 10.5% showed a sensitivity of 93.3% (LR^- = 0.138) for the exclusion of medium to large EV, and ICG-r15 ≥ 31.0% showed a specificity of 93.4% (LR^+ =6.06) for the diagnosis of medium to large EV. On the other hand, ICG-r15 < 7.5% showed a sensitivity of 93.8% (LR^- = 0.242) for the exclusion of high risk EV, and ICG-r15 ≥ 31.0% showed a specificity of 93.4% (LR^+ =5.68) for the diagnosis of high risk EV.

A total of 57 patients had ICG-r15 < 9.5%. Among them, four patients had EV, three had small varices (F_1), and one had medium varices (F_2). Furthermore, 60 patients had ICG-r15 < 10.5%, and only one of them had medium EV (s_2). The distribution of ICG-r15 for individuals is presented in Fig. 2.

4. DISCUSSION

To the best of our knowledge, this is the first study to demonstrate the performance of ICG-r15 for the prediction of EV in patients with HCC and to compare it with other noninvasive markers. For patients with HCC and preserved liver function, the ICG-r15 test is a simple, accurate, and clinically applicable noninvasive tool for selecting patients to avoid unnecessary endoscopic screening for EV. Up to 76.6% of our patients received curative treatment (mainly resection surgery (60.6%)) for HCC. This occurred because all the potential candidates for surgery routinely receive ICG-r15 for preoperation assessment in our hospital and most Eastern countries.[21,34] More patients with EV received non-curative treatment than patients without EV due to previous guidelines suggesting that liver resection surgery might only be performed for patients without portal hypertension.[35,36] Moreover, for patients who

Table 2.

Predictive value for EV

	AUROC	95% CI	*p*	−2 ln (L)	AIC
ICG	0.784	0.686–0.881	<0.001	77.889	79.889
INR	0.714	0.610–0.818	<0.001	131.487	133.487
Platelet count	0.764	0.662–0.866	<0.001	122.979	124.979
Spleen diameter	0.680	0.564–0.795	0.003	130.214	132.214
APRI	0.754	0.658–0.850	<0.001	129.829	131.829
AAR	0.530	0.414–0.647	0.617	139.944	141.944
MELD score	0.633	0.536–0.730	0.026	143.079	145.079
FIB-4	0.771	0.678–0.864	<0.001	129.566	131.566
Lok index	0.748	0.659–0.838	<0.001	123.335	125.335
Park index	0.765	0.664–0.866	<0.001	118.725	120.725
PSDR	0.777	0.674–0.881	<0.001	120.986	122.986
ALBI grade	0.644	0.539–0.749	0.016	136.253	138.253
ALBI–PLT score	0.703	0.603–0.804	0.001	128.456	130.456

ALBI grade = albumin–bilirubin grade; ALBI-PLT score = Albumin–bilirubin grade and platelet count; APRI = aspartate aminotransferase/platelet ratio index; AAR = aspartate aminotransferase/alanine aminotransferase ratio; AUROC = area under ROC curve; −2 ln(L) = the full model −2 ln likelihood; FIB= Fibrosis; ICG = indocyanine green; PSDR = platelet count/spleen diameter ratio.

Table 3.

ICG-r15 cutoff values for rule in and rule out EV and M/L EV

		ICG-r15	Sensitivity	Specificity	PPV	LR^+	NPV	LR^-
EV	Rule out	9.5	86.7	50.5	32.5	1.72	93.0	0.269
	Rule in	31.0	40.0	98.1	85.7	21.05	85.4	0.612
M/L EV	Rule out	10.5	93.3	48.4	18.2	1.80	98.3	0.138
	Rule in	31.0	40.0	93.4	42.9	6.06	92.7	0.642
HRV	Rule out	7.5	93.8	25.6	26.1	1.26	93.6	0.242
	Rule in	31.0	37.5	93.4	61.4	5.68	84.2	0.669

EV = esophageal varices; HRV = high-risk EV; ICG-r15, indocyanine green 15-minute retention; M/L EV = medium or large esophageal varices; LR^+ = positive likelihood ratio; LR^- = negative likelihood ratio; NPV = negative predictive values; PPV = positive predictive values.

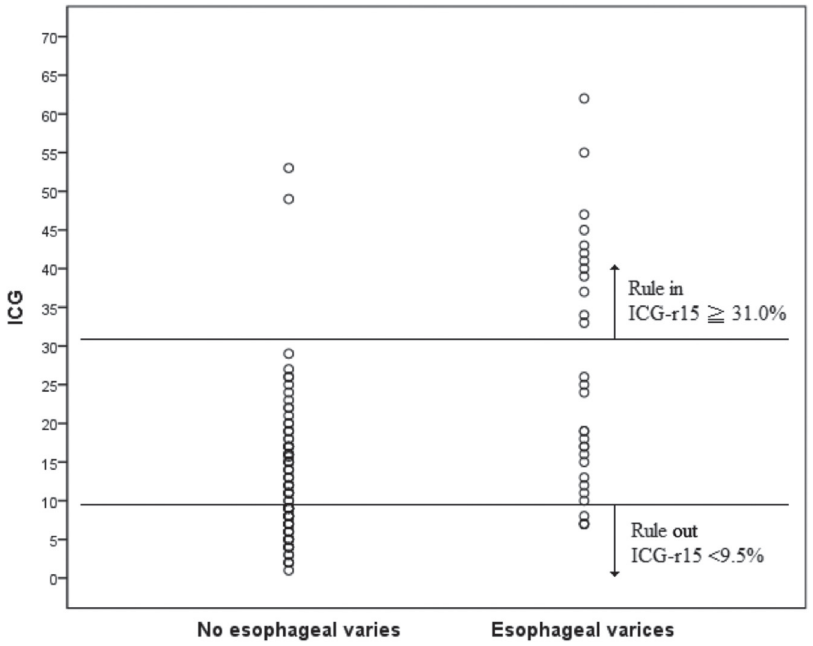

Fig. 2. Distribution of ICG-r15 among patients with and without esophageal varices. ICG-r15 = indocyanine green 15-minute retention test.

had HCC and EV (or significant portal hypertension), patients with smaller tumors are always selected as potential candidates for surgery.[29]

The rate of EV (21.9%) was relative low because we focused on patients with HCC and preserved liver function. The previous study from Taiwan showed 238 patients had EV with preserved liver function in a cohort of total 990 patients.[37] The rate of EV was 24.0% which is similar to our study.

Several non-invasive tools have been proposed to identify clinically significant portal hypertension, but most of them cannot be recommended for clinical use due to unreliable or inconsistent results.[38,39] Transient elastography seems to be the most promising tool for patients with cirrhosis. The Baveno VI consensus suggests that patients have a very low risk of high-risk varices requiring treatment and can avoid endoscopic screening if they have compensated advanced liver disease with liver stiffness < 20 kPa measured by transient elastography and a platelet count > 150,000.[15,40] However, the value of transient elastography in diagnosing EV in patients with HCC has not yet been determined because most of the transient elastography studies excluded patients with HCC.[16,41]

In this study, we particularly focused on patients with compensated liver function because ICG clearance has good correlation with HVPG in patients with preserved liver function.[25] However, anion excretion reserve may influence ICG clearance when liver function deteriorates. Our study suggests that the ICG-r15 has good performance for the prediction of EV, and it also had the best performance among the evaluated noninvasive markers.

Organic anion transporting polypeptide 1B3 (OATP1B3) and Na^+-taurocholate co-transporting polypeptide (NTCP) are involved in the transportation of ICG.[42] Previous studies demonstrated a reduction of OATP1B1 and OATP1B3 in patients with HCC.[26] Nevertheless, NTCP protein expression in HCC patients is higher than in cirrhosis patients.[27] These findings may explain the difference in ICG-r15 cutoff values for the diagnosis of EV between patients with cirrhosis and patients with HCC. However, more investigation is still needed for better understanding of the relationship between the transporters and HCC.

There are some limitations to our study. First, selection bias might be present because of the retrospective nature of the study. Second, the results could only apply to patients with HCC and preserved liver function. Third, our cohort included patients from 2007 onward, but our pathologist began reporting the Ishak score in 2010 in our hospital. Therefore, we could not compare the accuracy of ICG-r15 and the Ishak score in this study.

In conclusion, the ICG-r15 test has good performance for the prediction of EV in patients with HCC and compensated liver function. Thus, it could be used to assist clinicians in identifying patients with high risk of EV, reduce costs, and avoid unnecessary invasive endoscopy. However, further prospective studies are needed to validate the results.

REFERENCES

1. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study. *JAMA Oncol* 2017;**3**:1683–91.
2. D'Avola D, Iñarrairaegui M, Pardo F, Rotellar F, Marti P, Bilbao JI, et al. Prognosis of hepatocellular carcinoma in relation to treatment across BCLC stages. *Ann Surg Oncol* 2011;**18**:1964–71.
3. Walker M, El-Serag HB, Sada Y, Mittal S, Ying J, Duan Z, et al. Cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer. *Aliment Pharmacol Ther* 2016;**43**:621–30.
4. de Franchis R; Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010;**53**:762–8.
5. Giannini E, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. *Gut* 2003;**52**:1200–5.
6. Giannini E, Risso D, Botta F, Chiarbonello B, Fasoli A, Malfatti F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. *Arch Intern Med* 2003;**163**:218–24.
7. Thabut D, Imbert-Bismut F, Cazals-Hatem D, Messous D, Muntenau M, Valla DC, et al. Relationship between the fibrotest and portal

hypertension in patients with liver disease. *Aliment Pharmacol Ther* 2007;**26**:359–68.
8. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;**38**:518–26.
9. Lok AS, Ghany MG, Goodman ZD, Wright EC, Everson GT, Sterling RK, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. *Hepatology* 2005;**42**:282–92.
10. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology* 2007;**46**:32–6.
11. Park SH, Park TE, Kim YM, Kim SJ, Baik GH, Kim JB, et al. Non-invasive model predicting clinically-significant portal hypertension in patients with advanced fibrosis. *J Gastroenterol Hepatol* 2009;**24**:1289–93.
12. Sebastiani G, Tempesta D, Fattovich G, Castera L, Halfon P, Bourliere M, et al. Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: results of a multicenter, large-scale study. *J Hepatol* 2010;**53**:630–8.
13. Shi KQ, Fan YC, Pan ZZ, Lin XF, Liu WY, Chen YP, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. *Liver Int* 2013;**33**:62–71.
14. Castera L, Pinzani M, Bosch J. Non-invasive evaluation of portal hypertension using transient elastography. *J Hepatol* 2012;**56**:696–703.
15. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;**63**:743–52.
16. Qu Y, Li T, Ye Q, Zhang L, Wang L. A beginning or the end? A meta-analysis to assess the diagnostic accuracy of transient elastography for the prediction of esophageal varices. *Saudi J Gastroenterol* 2016;**22**:345–52.
17. Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. *J Clin Invest* 1960;**39**:592–600.
18. Levesque E, Martin E, Dudau D, Lim C, Dhonneur G, Azoulay D. Current use and perspective of indocyanine green clearance in liver diseases. *Anaesth Crit Care Pain Med* 2016;**35**:49–57.
19. Burczynski FJ, Pushka KL, Sitar DS, Greenway CV. Hepatic plasma flow: accuracy of estimation from bolus injections of indocyanine green. *Am J Physiol* 1987;**252**(5 Pt 2):H953–62.
20. Schneider PD. Preoperative assessment of liver function. *Surg Clin North Am* 2004;**84**:355–73.
21. Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. *Br J Surg* 2010;**97**:1260–8.
22. 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.
23. Zipprich A, Kuss O, Rogowski S, Kleber G, Lotterer E, Seufferlein T, et al. Incorporating indocyanin green clearance into the Model for End Stage Liver Disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. *Gut* 2010;**59**:963–8.
24. Lisotti A, Azzaroli F, Cucchetti A, Buonfiglioli F, Cecinato P, Calvanese C, et al. Relationship between indocyanine green retention test, decompensation and survival in patients with Child-Pugh A cirrhosis and portal hypertension. *Liver Int* 2016;**36**:1313–21.
25. Lisotti A, Azzaroli F, Buonfiglioli F, Montagnani M, Cecinato P, Turco L, et al. Indocyanine green retention test as a noninvasive marker of portal hypertension and esophageal varices in compensated liver cirrhosis. *Hepatology* 2014;**59**:643–50.
26. Vasuri F, Golfieri R, Fiorentino M, Capizzi E, Renzulli M, Pinna AD, et al. OATP 1B1/1B3 expression in hepatocellular carcinomas treated with orthotopic liver transplantation. *Virchows Arch* 2011;**459**:141–6.
27. Billington S, Ray AS, Salphati L, Xiao G, Chu X, Humphreys WG, et al. Transporter expression in noncancerous and cancerous liver tissue from donors with hepatocellular carcinoma and chronic hepatitis C infection quantified by LC-MS/MS proteomics. *Drug Metab Dispos* 2018;**46**:189–96.
28. Yamazaki S, Takayama T, Nakamura M, Higaki T, Matsuoka S, Mizuno S, et al. Prophylactic impact of endoscopic treatment for esophageal varices in liver resection: a prospective study. *J Gastroenterol* 2014;**49**:917–22.
29. Cucchetti A, Cescon M, Golfieri R, Piscaglia F, Renzulli M, Neri F, et al. Hepatic venous pressure gradient in the preoperative assessment of patients with resectable hepatocellular carcinoma. *J Hepatol* 2016;**64**:79–86.
30. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol* 2015;**33**:550–8.
31. Chen PH, Hsieh WY, Su CW, Hou MC, Wang YP, Hsin IF, et al. Combination of albumin-bilirubin grade and platelets to predict a compensated patient with hepatocellular carcinoma who does not require endoscopic screening for esophageal varices. *Gastrointest Endosc* 2018;**88**:230–239.e2.
32. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, et al. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc* 1981;**27**:213–8.
33. Akaike H. A new look at the statistical model identification. In: *Selected Papers of Hirotugu Akaike*. Springer; 1974:215–22.
34. Makuuchi M, Kosuge T, Takayama T, Yamasaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. *Semin Surg Oncol*. 1993;9:298–304.
35. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;**35**:421–30.
36. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005;**42**:1208–36.
37. Hsieh WY, Chen PH, Lin IY, Su CW, Chao Y, Huo TI, et al. The impact of esophagogastric varices on the prognosis of patients with hepatocellular carcinoma. *Sci Rep* 2017;**7**:42577.
38. Thabut D, Moreau R, Lebrec D. Noninvasive assessment of portal hypertension in patients with cirrhosis. *Hepatology* 2011;**53**:683–94.
39. Tafarel JR, Tolentino LH, Correa LM, Bonilha DR, Piauilino P, Martins FP, et al. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. *Eur J Gastroenterol Hepatol* 2011;**23**:754–8.
40. Maurice JB, Brodkin E, Arnold F, Navaratnam A, Paine H, Khawar S, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. *J Hepatol* 2016;**65**:899–905.
41. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011;**54**:650–9.
42. de Graaf W, Häusler S, Heger M, van Ginhoven TM, van Cappellen G, Bennink RJ, et al. Transporters involved in the hepatic uptake of (99m) Tc-mebrofenin and indocyanine green. *J Hepatol* 2011;**54**:738–45.