Use of indocyanine green for assessment of hepatic functional reserve in cirrhotic patients undergoing hepatic resection for hepatocellular carcinoma

Amr M. Aziz, Hosam E. Soliman, Mohamad T. Badawy, Marwa L. Helal, Morsi K.M. Abdu, Ahmad N. Sallam

Department of Hepatopancreatobiliary Surgery, National Liver Institute, Menoufia University, Menoufia, Egypt

Correspondence to Morsi K.M. Abdu, MBBCh, MSc, Department of Hepatopancreatobiliary Surgery, National Liver Institute, Menoufia university, Menoufia 5310002, Egypt.
Tel: +20 122 571 3986;
Fax: 2221729, 2234586(048);
e-mail: morsikamal94@gmail.com

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Background
The existence of cirrhosis has been traditionally considered a contraindication, particularly for extensive hepatectomy because mortality and morbidity rates are unacceptably high. Several institutions have reported liver reserve capacity assessment methods. In addition to the Child–Pugh classification, many reports have demonstrated methods for evaluating the liver reserve, including the indocyanine green retention value (ICG-R15) and ICG clearance test (ICG-K).
Aim
To investigate the use of indocyanine for assessment of hepatic functional reserve in cirrhotic patients undergoing hepatic resection for hepatocellular carcinoma (HCC) with respect to postoperative outcome to identify patients who are at risk of developing liver dysfunction.
Patients and methods
This was a prospective study performed on 50 patients with hepatic resection. Patients' demographic data, preoperative laboratory investigation, resection type, and postoperative outcomes and complications were recorded from our prospectively maintained database. Their liver function reserve was evaluated by (a) preoperative ICG clearance testing [Plasma Disappearance Rate (PDR), R15] on the day prior to elective liver resection for HCC, along with analysis of postoperative outcomes, and (b) CTComputed Tomograaphy (CT) volumetric measurement at NLI, Menoufia University, Egypt, from January 2019 to December 2021.
Results
A total of 50 patients [male: 37 (74%) and female: 13 (26%)] with a mean age of 57.74 ± 7.62 years were included in this study, including 17 (34%) nonanatomical liver resections and 33 (66%) anatomical liver resections. A total of 14 (28%) patients developed postoperative liver dysfunction after liver resection. ICG clearance was significantly associated with liver dysfunction. An optimal cutoff for preoperative ICG clearance to accurately predict liver dysfunction was PDR less than 17.6%/min and R15 more than 10.27%.
Conclusion
In cirrhotic patients undergoing liver resection for HCC, preoperative findings of ICG clearance test, along with other potential risk factors such as age, type of liver resections and future liver remnant, other liver function tests, Child's risk class, Model for End Stage Liver Disease score, and hemostasis, have to be considered before the decision of liver resection in these patients.

Keywords:
hepatocellular carcinoma, indocyanine green, liver cirrhosis, liver resection, posthepatectomy liver failure

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Introduction

The existence of cirrhosis has been traditionally considered a contraindication, particularly for extensive hepatectomy because mortality and morbidity rates are unacceptably high. Cirrhotic patients have metabolic, circulatory, and coagulation problems linked to the diminished capacity of the diseased liver [1]. Owing to advances in hepatic surgical technique, better perioperative care, and improvements in patient selection criteria, liver resection for patients with chronic liver diseases can now be performed with low morbidity and mortality [2–7]. The operative procedures are usually selected on the basis of liver

function and the location and extent of the tumor. In particular, as surgical procedures that involve resection of a large proportion of the liver, such as right (RHL) and extended (ERHL) right hepatic lobectomy, are occasionally associated with postoperative liver failure [8].

Jarnagin *et al*. [9] reported a frequency of posthepatectomy liver failure (PHLF) of 5% in a group of patients mainly without chronic liver disease, whereas the occurrence of PHLF can reach 20% in patients with chronic liver disease or cirrhosis [10,11]. PHLF is closely related to the volume and function of the remnant liver, and these two variables are the major determinants of the adequacy of future remnant liver after resection [12].

Several institutions have reported liver reserve capacity assessment methods [11,13–21]. In addition to the Child–Pugh classification [13], many reports have demonstrated methods for evaluating the liver reserve, including the indocyanine green retention value (ICG-R15) [14], ICG clearance test (ICG-K) [15], hippuric acid test (hippurate ratio) [11], lidocaine monoethylglycinexylidide test [16], aminopyrine breath test [17], and 99mTc-galactosylhuman serum albumin scintigraphy [18,19]. Blood tests, such as hyaluronic acid, type IV collagen 7 s, and type III procollagen-N-peptide, have also been used as markers of hepatic fibrosis due to cirrhosis [20]. Moreover, because the platelet count sensitively reflects the degree of hepatic fibrosis, and because ICR-R15 is a simple test, these two parameters have been considered useful as preoperative hepatic function evaluation factors, and they have been reported to be excellent predictors of postoperative death [21].

The ICG test, as a simple parameter, is considered to reflect the degree of hepatic dysfunction more accurately because of its high predictive value for postoperative outcome after liver resection [21]. ICG is a synthetic dye that binds completely to albumin and b-lipoprotein and is eliminated by the liver into the bile virtually unchanged without any extrahepatic metabolism or excretion [22]. Excretion of ICG is dependent on hepatic adenosine triphosphate concentration, and decreased levels may reflect reduced ability to regenerate after liver resection. The ICG retention value at 15 min (ICG-R15) after injection is ~10% in normal persons. A cutoff value for a safe major hepatectomy is 14%, although the cutoff may be higher for centers with more operative experience, patients with adequate remnant liver volume, and/or those with limited resections [23,24]. Therefore, in this study, we investigated the use of indocyanine for assessment of hepatic functional reserve in cirrhotic patients undergoing hepatic resection for hepatocellular carcinoma (HCC) with respect to postoperative outcome to identify patients who are at risk of developing liver dysfunction.

Patients and methods

From January 2019 to December 2021, 103 curative liver resections for hepatic HCC in cirrhotic patients were performed at the National Liver Institute, Department of HPB Surgery and Liver Transplantation, Menoufia University, Egypt. The study was approved by the National Liver Institute Ethical Committee. Our inclusion criteria were Child A according to Child–Pugh classification, patients with hepatitis C virus or hepatitis B virus infection, and patients with Model for End Stage Liver Disease (MELD) score less than or equal to 12. Our exclusion criteria were patients with extrahepatic metastasis, HCC in noncirrhotic patients, intrahepatic cholangiocarcinoma, and patients who did not have or refuse an ICG-R 15 test at the time of HCC diagnosis. A total of 53 patients were excluded from the study analysis because they did not meet the inclusion criteria: three patients with unknown cause of cirrhosis, five cases with intrahepatic cholangiocarcinoma (two of them were gallbladder carcinoma), two cases of fibrolamellar HCC, and 43 cases refused to participate in the study. Therefore, a total of 50 patients with hepatic resection were included in this study. Patients' demographic data, preoperative laboratory investigation, resection type, and postoperative outcomes and complications were recorded from our prospectively maintained database. Their liver function reserve was evaluated by (a) ICG (Aurogreen) manufactured by: AUROLAB 1 (Veerapanjan, Madurai, India). IC-GREEN is a sterile, lyophilized green powder containing 25 mg of ICG with no more than 5% sodium iodide. It is packaged with an aqueous solvent consisting of sterile water for injection used to dissolve the ICG. IC-GREEN is to be administered intravenously. The ICG concentration was carried out in the Department of Clinical Biochemistry and Molecular Diagnostics, National Liver Institute, Menoufia University. All patients received the ICG test the day before surgery. After the patient's weight and the values were taken, a single bolus dose of 0.5 mg/kg of ICG (dissolved in 10 ml sterile water) was administered intravenously into a peripheral vein of patients who were in a supine position within 10 s. Venous blood samples were drawn from another site 5, 10, and 15 min later to be read with a pulse spectrophotometer at 805 nm (SPEKOL 11, Analytic Jena AG, Kundendienst, Carl Zeiss, Germany). Results were expressed as the percentage of

ICG retained at 15 min after the injection. Calibration curve was prepared by diluting the initial concentration of ICG (2.5 mg/ml) with MilliQ water (EMD Millipore Corporation, Thermo Scientific, Massachusetts, USA) to concentrations of 5–10 mg/l–15 and 30 mg/l. A solution with 200 ml of ICG and 200 ml of the patient's blank serum were mixed together to obtain final standard concentrations of 2.5–30 mg/l. This range was chosen to be sure that absorbance readings from different subjects and clearance could be captured. There was a linear relationship between absorbance and concentration of ICG solution in serum according to the Beer-Lambert's law up 15 mg/l. All samples including standard solutions, blank samples, and postinjection serum samples were vortexed (mixing of samples) at high speed for 10 s for till mixing of solutes, and 400 μm of each was transferred into a cuvette of ultrasound spectrophotometer. Absorbance was read on SPEKOL 11, with wavelength set at 805 nm. Triplicate readings were taken for each blank, standard, and sample. The mean of three readings was calculated and used as the result. A standard curve of absorbance against standard concentrations was constructed and was used to calculate the concentrations of serially collected serum samples obtained for each patient. There were no adverse reactions during the course of our study.

(b) CTComputed Tomograaphy (CT) volumetric measurement of the entire patient liver and both of its lobes was achieved with the help of a noncommercial self-developed image postprocessing software (Medical Image Editor; Thomas Lange, BS, Deutsches Herzzentrum, Berlin, Germany) by two senior radiologists who were experienced in reading of CT of the liver.

PHLF was defined according to International Study Group of Liver Surgery as 'a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased International Normalized Ratio (INR) and concomitant hyperbilirubinemia on or after postoperative day 5' [25]. Follow-up visits were performed at 1-week, 4-week, and 3-month intervals unless any alert signs appeared.

A written informed consent was taken from every patient included in our study.

Statistical analysis

Data were presented as mean±SD and range where appropriate. Comparisons between groups were made using Fisher's exact test and one-way analysis of variance. Values of *P* less than 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS, version 21 software (SPSS Inc., Chicago, Illinois, USA).

Result

A total of 50 patients were included in this study, with 37 (74%) males and 13 (26%) females. The mean age of the patients was 57.7 ± 7.6 years, with a range of 29–70 years. Hepatitis C virus was shown to represent the most common cause of cirrhosis in 39 (78%) patients. Overall, 26 (52%) patients had comorbidities; diabetes mellitus in 30 (60%) patients, and hypertension in 26 (52%) patients.

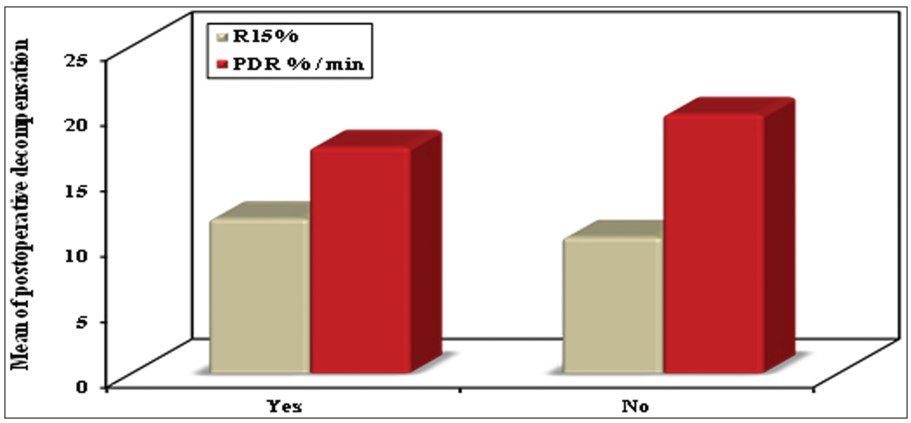
All patients were Child A class with a mean MELD score of 9.02 ± 1.82 (range, 6.0–14.0). The mean value of serum α–fetoprotein was 867.4 ± 4795.9 ng/dl (range, 5.70–34 000.0 ng/dl). A total of 16 (32%) patients had portal hypertension as defined by its surrogate markers such as splenomegaly, platelet count less than 100 000/cumm, and esophageal varices. In 26 (52%) patients, the maximum tumor diameter ranged from 3 to 5 cm, where more than 5 cm was seen in 23 (46%) patients and less than 3 cm in only one (2%) patients.

A total of 14 (28%) patients met the criteria of liver decompensation after they underwent liver resection. In these patients, the levels of Plasma Disappearance Rate (PDRs) were significantly lower than those of patients with liver function who recovered well [PDR: 17.25 ± 0.88%/min vs. 19.77 ± 1.89%/min (t=4.755, P<0.001)], as shown in Fig. 1. In contrast, the levels of ICG-R15 were significantly higher in patients with liver decompensation. The mean level of ICG-R15 was found to be 11.79 ± 1.24 vs. 10.37 ± 1.10% (t=3.946, P<0.001).

In univariate analysis, the preoperative factors that showed a statistically significant association with postoperative liver decompensation were age more than or equal to 60 years (P=0.030), diabetes mellitus DM (P=0.014), hepatitis B (P=0.001), preoperative serum albumin (as an indicator of the liver synthetic function) (P=0.031), ICG clearance test (ICG-R15 and PDR) (P=0.002), preoperative Prothrombin time (PT%) (as an indicator of liver biosynthetic activity) (P=0.031), Child risk class, MELD score (P≤0.001), portal hypertension (P=<0.001), bilobar lesions (P=0.025), multiple HCC two or more (P=0.002), as well as Barcelona Clinic Liver Cancer (BCLC) stage B (P=0.002) (Table 1b).

The operative factors that showed a statistically significant associated with postoperative liver

Figure 1



Relation between ICG clearance and liver dysfunction. ICG, indocyanine green.

decompensation were anatomical resection of more than two segments (*P*=0.032) and intraoperative blood loss (*P*=0.001) (Table 2).

Postoperative parameters significantly associated with postoperative liver decompensation were grade III HCC (*P*≤0.001), presence of microvascular invasion (*P*≤0.001), and HCC TNM stage II (*P*≤0.001) (Table 3).

In a multivariable analysis, ICG (PDR), PDR [odds ratio (OR)=0.204; 95% confidence interval (CI) 0.043–0.964; *P*=0.045), and blood loss (OR=1.008; 95% CI 1.000–1.016; *P*=0.049) remained with a significantly increased risk for liver decompensation in multivariable logistic regression analysis (Table 4).

In our study, the Youden-index was used to determine the optimal cut-off value for ICG-R15 and PDR for predicting liver decompensation following hepatectomy for HCC in our patients. This value for PDR was less than 17.6%/min and for R15 was more than 10.27%. The patients with impaired ICG clearance were significantly of older age (≥60 years). Impaired ICG-R15 was significantly associated with DM (*P*<0.001), portal hypertension (*P*=0.011), preoperative PT% (*P*=0.008), preoperative total bilirubin (*P*=0.011), platelet count, serum creatinine, and Child's risk class (A6) (*P*=0.032). Impaired PDR was significantly associated with all previous parameters including portal hypertension (*P*<0.001), INR (*P*=0.049), total serum bilirubin (*P*=0.012), and Child's risk class (A6) (*P*<0.001) in addition to viral hepatitis B (*P*<0.001), MELD score (mean, 10.28 ± 1.81) (*P*<0.001), bilobar lesions (*P*=0.033), BCLC stage (*P*=0.001), and type of resection [anatomical (>2 segments) (*P*=0.001)]. Blood loss and prolonged operative time (*P*<0.001) were also significantly associated with impaired PDR. Postoperative liver decompensation was significantly associated with impaired both ICG-R15 (*P*=0.031) and PDR (*P*<0.001), which resulted in more complications and prolonged hospitalization (Table 5a,b).

Regarding the validity [area under a curve (AUC), sensitivity, and specificity] of ICG clearance, the sensitivity for R15 (>10.27%) was 85.71% and the specificity was 47.22% [positive predictive value (PPV): 38.7% and negative predictive value (NPV): 89.5%], and for PDR (<17.6%/min), the sensitivity was 92.86% and specificity was 86.7 (PPV: 72.2% and NPV: 96.9%), as shown in Table 6 and Fig. 2.

Discussion

PHLF/I is the most appalling complication of liver resection. It is seldom reversible and results in significant postoperative morbidity and mortality. The prediction of PHLF/I today is still a science in evolution, with qualitative and quantitative assessment of future liver remnant (FLR) representing the basis for most predictive models in previous studies [26].

The predictive risk factors of PHLF can be categorized into patient related, liver related, and surgery related.

In our study, the preoperative predictive risk factors for PHLF were age (>60) (*P*=0.030), DM (*P*=0.014), viral hepatitis B (*P*=0.001), preoperative serum albumen (*P*=0.031), preoperative PT % (*P*=0.031), Child's class A score 6 (*P*≤0.001), MELD score more than 10 (*P*≤0.001), and ICG clearance test (ICG-R15 and PDR) (*P*=0.002).

The effect of ageing on liver functions is unclear and is vaguely elucidated to be related to factors such as reduced capacity to produce acute-phase reactants and decrease in basal and taurocholate-stimulated bile flow [26]. In a study on 775 patients, Balzan *et al.* [27] found

Table 1 Univariate logistic regression analysis for liver decompensation regarding to preoperative factors

(a) Univariate analysis for liver decompensation regarding preoperative factors				
Variables	Liver decompensation [*n* (%)]		Univariate	
	No (*N*=36)®;	Yes (*N*=14)	OR (95% CI)	*P*
Sex				
Male	26 (72.2)	11 (78.6)	1.410 (0.324–6.135)	0.647
Female	10 (27.8)	3 (21.4)	0.709 (0.163–3.085)	0.647
Age (years)				
<60®	23 (63.9)	4 (28.6)	1.000	0.030*
≥60	13 (36.1)	10 (71.4)	4.423 (1.153–16.964)	
HCV				
No®	10 (27.8)	1 (7.1)	1.000	0.144
Yes	26 (72.2)	13 (92.9)	5.000 (0.576–43.388)	
HBsAg				
No®	30 (83.3)	4 (28.6)	1.000	0.001*
Yes	6 (16.7)	10 (71.4)	12.500 (2.922–53.478)	
DM				
No®	19 (52.8)	1 (7.1)	1.000	0.014*
Yes	17 (47.2)	13 (92.9)	14.529 (1.715–123.07)	
Hypertension				
No®	19 (52.8)	5 (35.7)	1.000	0.282
Yes	17 (47.2)	9 (64.3)	2.012 (0.563–7.193)	
Albumin	3.89 ± 0.55	3.48 ± 0.57	0.271 (0.083–0.887)	0.031*
PLT	158.4 ± 51.9	156.8 ± 45.73	0.999 (0.987–1.012)	0.918
ICG-R15%	10.37 ± 1.10	11.79 ± 1.24	2.633 (1.409–4.920)	0.002*
ICG-PDR (%/min)	19.77 ± 1.89	17.25 ± 0.88	0.166 (0.054–0.507)	0.002*
PT%	78.92 ± 10.4	71.32 ± 10.08	0.927 (0.866–0.993)	0.031*
Total bilirubin	0.82 ± 0.45	1.10 ± 0.45	3.480 (0.908–13.336)	0.069
Direct bilirubin	0.36 ± 0.22	0.42 ± 0.28	3.191 (0.252–40.368)	0.370
AFP				
<200	30 (83.3)	12 (85.7)	1.200 (0.212–6.801)	0.837
≥200	6 (16.7)	2 (14.3)	0.833 (0.147–4.723)	0.837
Child's risk class				
A5®	29 (80.6)	1 (7.1)	1.000	<0.001*
A6	7 (19.4)	13 (92.9)	53.857 (5.99–483.65)	
MELD score				
<10®	35 (97.2)	1 (7.1)	1.000	<0.001*
≥10	1 (2.8)	13 (92.9)	455.0 (26.47-7818.6)	
Portal hypertension				
No®	33 (91.7)	1 (7.1)	1.00	<0.001*
Yes	3 (8.3)	13 (92.9)	143.0 (13.60- 1503.0)	
(b) Univariate analysis for liver decompensation regarding preoperative factors				
Preoperative imaging and staging				
Liver parenchyma				
Periportal fibrosis	15 (41.7)	0	–	1.000
Mixed	13 (36.1)	0	–	0.998
Cirrhosis	8 (22.2)	14 (100.0)	–	
Tumor site				
Right lobe	18 (50.0)	7 (50.0)	1.000 (0.29–3.437)	1.000
Left lobe	17 (47.2)	3 (21.4)	0.305 (0.07–1.279)	0.105
Bilobar	1 (2.8)	4 (28.6)	14.0 (1.40–139.81)	0.025*
Max. tumor diameter	5.74 ± 2.65	6.44 ± 3.28	1.087 (0.88–1.341)	0.434
Number of tumor				
1®	34 (94.4)	7 (50.0)	1.000	0.002*
2	2 (5.6)	7 (50.0)	17.00 (2.89–99.75)	
Macrovascular invasion				
No	36 (100.0)	12 (85.7)	-	-
Yes	0	2 (14.3)	–	0.999

Table 1 Continued

Variables	Liver decompensation [*n* (%)]		Univariate	
	No (*N*=36)®;	Yes (*N*=14)	OR (95% CI)	*P*
CT volumetry				
Left lobe % (*N*=34)	(*N*=23) 35.52±8.04	(*N*=11) 32.02±4.62	0.912 (0.794–1.047)	0.190
Right lobe % (*N*=34)	(*N*=24) 55.55±6.94	(*N*=10) 55.58±4.27	1.001 (0.887–1.129)	0.993
Milan criteria				
Beyond	16 (44.4)	8 (57.1)	1.667 (0.47–5.794)	0.422
Within	20 (55.6)	6 (42.9)	0.600 (0.17–2.086)	0.422
BCLC				
A	34 (94.4)	7 (50.0)	1.000	0.002*
B	2 (5.6)	7 (50.0)	17.0 (2.89–99.75)	

CI, confidence interval; DM, diabetes mellitus; HCV, hepatitis C virus; MELD, Model for End Stage Liver Disease; OR, odds ratio; ®, reference; AFP, Alfa Feto Protein; PLT, Platelet. *Statistically significant at *P* value less than or equal to 0.05.

Table 2 Univariate logistic regression analysis for liver decompensation regarding operative data

Variables	Liver decompensation [*n* (%)]		Univariate	
	No (*N*=36)®	Yes (*N*=14)	OR (95% CI)	*P*
Operative data				
Type of operation				
Open	28 (77.8)	14 (100.0)	–	
Laparoscopic	8 (22.2)	0	0	0.999
Type of resection				
Anatomical	20 (55.6)	13 (92.9)	10.400 (1.227–88.178)	0.032*
Nonanatomical®;	16 (44.4)	1 (7.1)	1.000	
Operative time (min)	140.5±20.16	241.8±48.54	1.285 (0.942–1.753)	0.114
Intraoperative blood loss	483.3±300.9	1046.4±228.3	1.007 (1.003–1.012)	0.001*

CI, confidence interval; OR, odds ratio; ®, Reference.

Table 3 Univariate logistic regression analysis for liver decompensation regarding postoperative data

Variables	Liver decompensation [*n* (%)]		Univariate	
	No (*N*=36)®	Yes (*N*=14)	OR (95% CI)	*P*
Postoperative data				
Grading				
II®	31 (86.1)	2 (14.3)	1.000	
III	5 (13.9)	12 (85.7)	37.20 (6.336–218.406)	<0.001*
Microvascular invasion				
No®	31 (86.1)	4 (28.6)	1.000	
Yes	5 (13.9)	10 (71.4)	15.50 (3.474–69.159)	<0.001*
TNM stage				
I	31 (86.1)	3 (21.4)	1.000	
II	5 (13.9)	11 (78.6)	22.733 (4.645–111.262)	<0.001*
Hospital stay (days)	18.57±5.14	6.61±1.92	–	0.987

CI, confidence interval; OR, odds ratio; ®, reference. *Statistically significant at *P* value less than or equal to 0.05.

Table 4 Multivariate logistic regression analysis for liver decompensation regarding different parameters

Variables	OR (95% CI)	*P*
R15%	0.637 (0.191–2.118)	0.461
PDR%/min	0.204 (0.043–0.964)	0.045*
Type of resection (anatomical)	1.013 (0.204–5.040)	0.988
Intraoperative blood loss	1.008 (1.000–1.016)	0.049*
Age (≥60 years)	0.957 (0.085–10.834)	0.972
PT% preoperative	1.024 (0.909–1.154)	0.695

CI, confidence interval; OR, odds ratio; *P*, *P* value for OR for comparing between liver decompensation and non-liver decompensation. *Statistically significant at *P* value less than or equal to 0.05

Table 5 The optimal cut-off value for ICGR15 and PDR for predicting liver decompensation following hepatectomy for HCC in our patients using Youden-index

(a) Relation between ICG clearance cutoff values and different parameters

	R15%		*P*	PDR		*P*
	≤10.27 (*N*=19) [*n* (%)]	>10.27 (*N*=31) [*n* (%)]		≤17.6 (*N*=18) [*n* (%)]	>17.6 (*N*=32) [*n* (%)]	
Sex						
Male	16 (84.2)	21 (67.7)	0.320	13 (72.2)	24 (75.0)	1.000
Female	3 (15.8)	10 (32.3)		5 (27.8)	8 (25.0)	
Age (years)						
Mean±SD	57.95±5.97	57.61±8.57	0.882	58.17±7.06	57.50±8.02	0.770
Median (min.–max.)	55.0 (50.0–67.0)	60.0 (29.0–70.0)		61.0 (40.0–65.0)	58.0 (29.0–70.0)	
Weight (kg)						
Mean±SD	71.42±5.45	71.23±5.21	0.900	71.17±4.84	71.38±5.53	0.894
Median (min.–max.)	70.0 (64.0–82.0)	71.0 (62.0–82.0)		71.0 (64.0–80.0)	70.50 (62.0–82.0)	
DM	6 (31.6)	24 (77.4)	0.001*	18 (100.0)	12 (37.5)	0.001*
Hypertension	10 (52.6)	16 (51.6)	1.000	12 (66.7)	14 (43.8)	0.119
HCV	12 (63.2)	27 (87.1)	0.078	17 (94.4)	22 (68.8)	0.072
HBV	4 (21.1)	12 (38.7)	0.194	12 (66.7)	4 (12.5)	0.001*
Portal hypertension	2 (10.5)	14 (45.2)	0.011*	14 (77.8)	2 (6.3)	0.001*
Preoperative laboratory data						
Albumin						
Mean±SD	3.87±0.58	3.71±0.57	0.343	3.58±0.62	3.88±0.53	0.079
Median (min.–max.)	4.0 (2.20–4.60)	3.80 (2.60–4.90)		3.40 (2.60–4.90)	4.0 (2.20–4.60)	
AST						
Mean±SD	67.79±53.14	58.06±28.78	0.575	60.89±29.65	62.25±44.66	0.460
Median (min.–max.)	62.0 (26.0–266.0)	50.0 (21.0–151.0)		51.50 (21–151)	45.0 (26.0–266.0)	
ALT						
Mean±SD	50.74±30.74	42.45±23.21	0.496	49.17±25.48	43.59±26.99	0.284
Median (min.–max.)	36.0 (17.0–117.0)	39.0 (11.0–104.0)		45.50 (12–104)	36.0 (11.0–117.0)	
PT%						
Mean±SD	80.91±10.96	74.27±9.97	0.008*	72.15±9.47	79.40±10.68	0.001*
Median (min.–max.)	82.0 (64.70–98.0)	72.0 (57.50–95.8)		69.80 (57.5–86.2)	80.10 (61.4–98.0)	
Total bilirubin						
Mean±SD	0.73±0.47	1.0±0.44	0.011*	1.09±0.47	0.79±0.44	0.012*
Median (min.–max.)	0.59 (0.32–2.40)	0.90 (0.34–1.90)		1.0 (0.42–1.90)	0.68 (0.32–2.40)	
Direct bilirubin						
Mean±SD	0.31±0.19	0.41±0.26	0.362	0.40±0.27	0.36±0.22	0.700
Median (min.–max.)	0.30 (0.10–0.93)	0.30 (0.10–0.96)		0.30 (0.10–0.96)	0.30 (0.10–0.93)	
INR						
Mean±SD	1.13±0.21	1.21±0.18	0.193	1.27±0.26	1.13±0.13	0.049*
Median (min.–max.)	1.08 (0.89–1.86)	1.14 (1.0–1.86)		1.19 (1.02–1.86)	1.10 (0.89–1.40)	
Creatinine						
Mean±SD	1.05±0.37	1.67±0.76	0.002*	2.20±0.57	1.0±0.26	0.001*
Median (min.–max.)	0.98 (0.78–2.43)	1.50 (0.53–3.08)		2.10 (0.98–3.08)	0.98 (0.53–1.80)	
Platelet						
Mean±SD	152.6±29.73	132.2±39.35	0.043*	108.3±33.24	157.8±25.60	0.001*
Median (min.–max.)	148.0 (76–202)	134.0 (76–203)		94.5 (76.0–180.0)	151.5 (107 –203)	
AFP						
Mean±SD	236.7±476.8	1253.9±6084.9	0.424	2063.7±7975.5	194.5±419.3	0.903
Median (min.–max.)	75.3 (6.20–1809)	39.8 (5.7–34000)		35.4 (5.9–34000)	43.5 (5.70–1809)	

Table 5 Continued

(b) Relation between ICG clearance cutoff values and different parameters

Variables	R15%		*P*	PDR		*P*
	≤10.27 (*N*=19) [*n* (%)]	>10.27 (*N*=31) [*n* (%)]		≤17.6 (*N*=18) [*n* (%)]	>17.6 (*N*=32) [*n* (%)]	
Child's risk class						
A5	15 (78.9)	15 (48.4)	0.032*	2 (11.1)	28 (87.5)	*P*<0.001*
A6	4 (21.1)	16 (51.6)		16 (88.9)	4 (12.5)	
MELD score						
Mean±SD	8.63±1.26	9.16±1.92	0.244	10.28±1.81	8.22±1.10	*P*<0.001*
Median (min.–max.)	8.0 (7.0–11.0)	9.0 (6.0–13.0)		10.50 (7.0–13.0)	8.0 (6.0–11.0)	
Tumor site						
Right lobe	8 (42.1)	17 (54.8)		10 (55.6)	15 (46.9)	
Left lobe	10 (52.6)	10 (32.3)	0.362	4 (22.2)	16 (50.0)	*P*=0.033*
Bilobar	1 (5.3)	4 (12.9)		4 (22.2)	1 (3.1)	
Tumor size						
≤3 cm	1 (5.3)	0		0	1 (3.1)	
3–5 cm	10 (52.6)	16 (51.6)	*P*=0.612	10 (55.6)	16 (50.0)	*P*=1.000
>5 cm	8 (42.1)	15 (48.4)		8 (44.4)	15 (46.9)	
Mean±SD	5.93±2.98	5.95±2.77	*P*=0.734	6.10±3.05	5.85±2.73	*P*=0.678
Median (min.–max.)	4.90 (3.0–15.0)	5.0 (3.20–16.0)		5.0 (3.40–16.0)	5.0 (3.0–15.0)	
MILAN criteria						
Within	12 (63.2)	14 (45.2)	*P*=0.216	8 (44.4)	18 (56.3)	*P*=0.423
Beyond	7 (36.8)	17 (54.8)		10 (55.6)	14 (43.8)	
BCLC stage						
A	18 (94.7)	23 (74.2)	*P*=0.127	10 (55.6)	31 (96.9)	*P*=0.001*
B	1 (5.3)	8 (25.8)		8 (44.4)	1 (3.1)	
Type of resection						
Anatomical	12 (63.2)	21 (67.7)	*P*=0.740	17 (94.4)	16 (50.0)	*P*=0.001*
Nonanatomical	7 (36.8)	10 (32.3)		1 (5.6)	16 (50.0)	
Blood loss						
Mean±SD	519.5±350.3	715.5±382.1	*P*=0.080	972.2±235.3	454.7±311.9	*P*<0.001*
Median (min.–max.)	450 (150–1200)	750 (100–1250)		1050 (450–1250)	425 (100–1200)	
Operative time						
Mean±SD	154.1±51.91	177.9±55.70	*P*=0.139	211.1±57.92	145.1±36.38	<0.001*
Median (min.–max.)	135 (106–310)	155 (110–305)		207.5 (125–305)	137.5 (106–310)	
Decompensation	2 (10.5)	12 (38.7)	*P*=0.031*	13 (72.2)	1 (3.1)	*P*<0.001*
Clavien-Dindo grade						
No complications	10 (52.6)	11 (35.5)		0	21 (65.6)	
Grade I	4 (21.1)	17 (54.8)		16 (88.9)	5 (15.6)	
Grade IIIa	4 (21.1)	1 (3.2)		1 (5.6)	4 (12.5)	
Grade IIIb	1 (5.3)	0	*P*=0.023*	0	1 (3.1)	*P*<0.001*
Grade Iva	0	1 (3.2)		0	1 (3.1)	
Grade IVb	0	0		0	0	
Grade V	0	1 (3.2)		1 (5.6)	0	
Hospital stay duration						
Mean±SD.	8.05±3.32	11.13±7.31	*P*=0.416	15.50±7.17	6.84±2.38	*P*<0.001*
Median (min.–max.)	7.0 (4.0–17.0)	8.0 (4.0–30.0)		15.50 (4.0–30.0)	7.0 (4.0–15.0)	

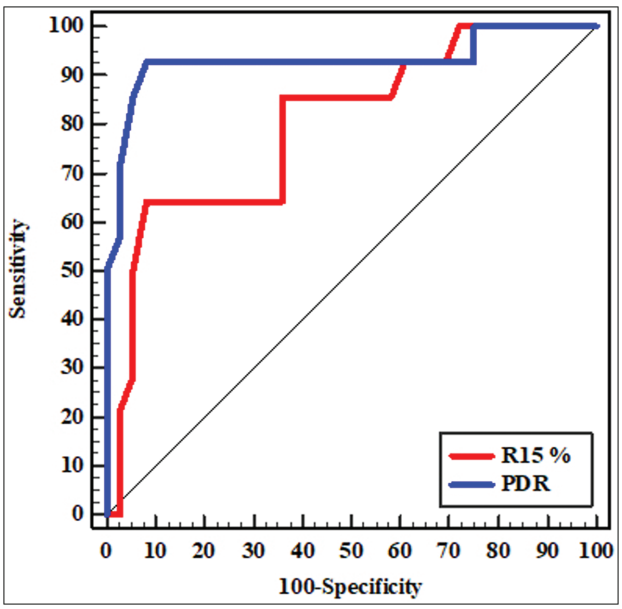
χ^2, χ^2 test; DM, diabetes mellitus; FE, Fisher exact; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End Stage Liver Disease; *P*, *P* value for comparing between the different categories; *t*, Student *t* test; *U*, Mann–Whitney test; AST, Aspartate amino transfrase; ALT, Alanine amino transfrase. *Statistically significant at *P* value less than or equal to 0.05.

Table 6 Validity (area under a curve, sensitivity, and specificity) for R15% and PDR to predict liver decompensation

	AUC	*P*	95% CI	Cut off	Sensitivity	Specificity	PPV	NPV
R15%	0.799	0.001*	0.659–0.938	>10.27	85.71	47.22	38.7	89.5
PDR	0.931	<0.001*	0.827–1.034	≤17.6	92.86	86.11	72.2	96.9

AUC, area under a curve; CI, confidence intervals; NPV, negative predictive value; PPV, positive predictive value. *Statistically significant at *P* value less than or equal to 0.05.

Figure 2



Receiver operating characteristic curve for R15% and PDR to predict liver dysfunction (*n*=14 vs. 35).

age more than 65 years to be an independent predictor of mortality after hepatectomy. Kim *et al.* [28] in their study on 279 patients undergoing partial hepatectomy reported no correlation of age with the postoperative outcome.

Role of insulin as a potent hepatotrophic factor [stimulation of Insulin Growth Factor (IGF) and Hepatocyte Growth Factors (HGFs)] has been quoted widely [29]. Bucher reported a higher incidence of hepatic atrophy with insulin depletion in their study on animal models [30]. Similarly, Fan *et al.* [31] demonstrated a correlation of malnutrition with higher incidence of PHLF in their prospective series of 124 patients undergoing hepatectomy.

According to AASLD and EALD, only Child A patients with resectable HCC are candidates for hepatic resection and Child B and C patients with early stage HCC are better served with transplantation [32,33]. Patients with cirrhosis and acute viral hepatitis have even higher mortality [34].

In a series of 2056 patients, Hyder *et al.* [35] have reported a higher risk of mortality and PHLF with MELD more than 10 (P<0.001). However, Rahbari *et al.* [36] reported a sensitivity of only 51 and 70% of MELD score for predicting morbidity and mortality, respectively. A worse ICG clearance was associated with the development of postoperative liver dysfunction. These results are in accordance with previous smaller studies [12,37,38]. Gu *et al.* [39] found that preoperative ICG-R15 achieved an AUC receiver operating characteristic (ROC) of 0.657 and 0.640 for the prediction of PHLF and 90-day mortality, respectively. Wong *et al.* [40] failed to achieve any significant prediction of postoperative severe morbidity using preoperative ICG-R15 (AUC ROC=0.51). Wang *et al.* [41] found that preoperative ICG-R15 surpassed both CTP score and MELD for the prediction of severe PHLF, but with moderate AUC ROC=0.724.

In our study, operative factors with a statistically significant association with postoperative liver decompensation were anatomical resection of more than two segments (P=0.032) and intraoperative blood loss (P=0.001).

Excess intraoperative blood loss (>1200 ml) is associated with intravascular fluid shifts that may induce bacterial translocation with resultant systemic inflammation and coagulopathy, predisposing to PHLF [42]. In a study on 1056 patients undergoing hepatectomy, Imamura *et al.* [43] found a strong association between intraoperative blood loss (>1000 ml) and incidence of postoperative complications. The earliest description of 'small for size syndrome' dates to 1996, when Emond *et al.* [44] defined this entity as graft recipient weight ratio less than 0.8–1.0 or less than 30–50% of standard/estimated liver volumes. Small for size syndrome exerts its deleterious effect on the liver parenchyma by causing hemodynamic changes in the form of increase in portal pressure with resultant increase in intrasinusoidal pressures and hepatocyte damage. Hence, two important determinants for hepatectomy are (a) FLR volume/standardized liver volume ratio, preferably more than 20%, and (b) body weight ratio of liver volume, with 0.5 set as the threshold value. These have been found to be highly predictive of PHLF [45].

In a multivariable analysis, ICG-PDR (OR=0.204; 95% CI 0.043–0.964; P=0.045) and blood loss (OR=1.008; 95% CI 1.000–1.016; P=0.049) remained significantly associated with increased risk for liver decompensation.

The optimal cutoff value for PDR was less than 17.6%/min and for R15 was more than 10.27%. The patients with impaired ICG clearance were significantly of older age (≥60 years). Impaired ICG-R15 was significantly associated with DM (P<0.001), portal hypertension (P=0.011), preoperative PT% (P=0.008), preoperative total bilirubin (P=0.011), platelet count, serum creatinine, and Child's risk class (A6) (P=0.032). Impaired PDR was significantly associated with previous parameters including portal hypertension (P<0.001), INR (P=0.049), total serum bilirubin (P=0.012), and Child's risk class (A6) (P<0.001)

in addition to viral hepatitis B (P<0.001), MELD score (mean, 10.28 ± 1.81) (P<0.001), bilobar lesions (P=0.033), BCLC stage (P=0.001), and type of resection (anatomical (>2 segments) (P=0.001). Blood loss and prolonged operative time (P<0.001) were also significantly associated with impaired PDR. The sensitivity for R15 (>10.27%) was 85.71% and the specificity was 47.22% (PPV: 38.7%; NPV: 89.5%). For PDR (<17.6%/min), the sensitivity was 92.86% and specificity was 86.7% (PPV: 72.2%; NPV: 96.9%).

A study by Schwarz *et al.* [46] reported that patients with a worse ICG clearance were generally older, more likely to be male, and had a higher grade of liver fibrosis in the resected specimen compared with patients with normal values. Moreover, the studies by Zipprich *et al*. [47] and Danin *et al*. [48] showed a connection between ICG clearance and liver fibrosis.

ICG-clearance and ICG-PDR are highest in the preoperative liver (resection rate=0) and decrease with increasing resection rate, whereas ICG-t1=2 and ICG-R15 are lowest in the healthy liver and increase with increasing resection rate. The effect of varying the degree of cirrhosis is in accordance with the results. Importantly, increasing resection rate and increasing degree of cirrhosis affect ICG pharmacokinetic parameters in the same manner. The dependencies of ICG-clearance, ICG-PDR, ICG-t1=2, and ICG-R15 on the resection rate are fairly linear up to 50–60% resection and become much more nonlinear for higher resection rates [49].

Thomas and colleagues found a significant correlation between posthepatectomy ICG-PDR and intraoperative ICG-PDR measured under trial clamping of those parts of the liver that were to be removed. This was simulated by changing hepatic blood flow and liver volume in separate simulations but in the same intervals. This was performed for a healthy liver as well as three different degrees of cirrhosis. The predictions agree well with the clinical data and show that reducing hepatic blood flow (clamping of liver volumes which will be resected) has a very similar effect on ICG elimination as actually removing the respective liver volume via hepatectomy [50].

The cutoff of ICG-R15 less than 20% allows to identify low-risk patients that are unlikely to have poor postoperative outcome after partial hepatectomy. This was confirmed by the high negative and low PPV (80 and 30%, respectively), suggesting that ICG-R15 is especially useful for the identification of low-risk patients. A recommendation was that patients with ICG-R15 20–40% should undergo a more careful evaluation of the treatment options, and additional information should be taken into consideration [49].

Schwarz *et al.* [46] reported that their study patients with HCC had a significantly impaired ICG clearance compared with patients with other indications for liver resection (metastasis, cholangiocarcinoma, or benign disease) [PDR: 19.5%/min (16.4–25) vs. 21.6%/min (18–25.7); P=0.009]. Additionally, patients with HCC a significantly higher fibrosis score in the resected specimen.

The study by de Liguori Carino *et al*. [37] reported that when the preoperative ICG-PDR was less than 17.6%/min and the preoperative serum bilirubin was more than 17 μmol/l, the PPV for postoperative liver dysfunction was 75% and the negative predictive value was 90%.

Scheingraber *et al.* [51] reported that PDR (ICG) and PT but not bilirubin preoperatively differentiated between patients with and without cirrhosis. In cirrhosis, PDR (ICG) patients did not recover to preoperative baseline values. ROC analysis revealed that PDR (ICG) did significantly better indicate postoperative liver dysfunction than bilirubin and PT.

Conclusion

In cirrhotic patients undergoing liver resection for HCC, preoperative findings of ICG clearance test along with other potential risk factors such as age, type of liver resections, and FLR, other liver function tests, Child's risk class, MELD score, and hemostasis, have to be considered before the decision of liver resection in these patients.

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Conflicts of interest

No conflict of interest.

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