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Original article

Comparison of indocyanine green clearance test and Child-Pugh score in evaluation of pre-hepatectomy liver function

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Abstract: ***Introduction:*** Indocyanine green (ICG) clearance (through ICG retention rate at 15 minutes - ICG-R15) is proven to correlate with histological fibrosis stage. Child-Pugh score, although proven to have weaker correlation, is still one of pre-hepatectomy liver function assessments. This study is to compare ICG-R15 and Child-Pugh score in evaluation of histological fibrosis stage and predicting of post-hepatectomy liver failure (PHLF) and to create the model of staging estimation for fibrosis. ***Methods:*** A prospective cohort study was conducted in 340 patients of hepatectomy. ICG-R15, Child-Pugh score and platelet count (PLT) were analyzed to examine their association with histological fibrosis stage and PHLF. Ordinal logistic regression was used to establish the model of staging estimation for fibrosis. ***Results:*** Child-Pugh score showed no significant association with histological fibrosis stage ($p = 0.257$) while ICG-R15 had a weak correlation ($r = 0.232$, $p < 0.001$), INR had a weak correlation ($r = 0.156$, $p = 0.004$), PLT had a negative correlation ($r = -0.378$, $p < 0.001$). The histological fibrosis stage could be estimated based on gender, age, ICG-R15 and PLT with AUC of 0.68. ICG-R15 was shown to be related to PHLF ($p = 0.039$) in which non-PHLF group had 0.75 times lower ICG-R15 than PHLF group while Child-Pugh score was shown to be statistically insignificant. ***Conclusion:*** ICG clearance test was better than Child-Pugh score in evaluation of pre-hepatectomy liver function and predicting of PHLF. It was possible to estimate the histological fibrosis stage based on gender, age, ICG-R15 and PLT.

Keywords: Indocyanine green clearance; ICG-R15; hepatectomy; post-hepatectomy liver failure; PHLF.

1. INTRODUCTION

Evaluation of pre-hepatectomy liver function is a very important step to predict and prevent severe PHLF which has low incidence of 0 - 5.1% (1-7) but high mortality rate, up to 75% (2). Although Child-Pugh score was shown to have insignificant correlation to histological fibrosis stage in Child-

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Pugh A patients (8), this is still one of the criteria of assessing pre-hepatectomy liver function (9, 10).

ICG-R15 is considered as one of the best liver function tests and applied worldwide, especially in Asia - Pacific regions and becomes one of the standards for decision of the indication and the extent of liver resection (9, 11-13).

ICG-R15 has a close correlation to liver function deficiency and portal hypertension (14-18) as well as the progression to decompensated cirrhosis (19). Almost all patients undergoing hepatectomies are in Child-Pugh class A. For those patients, ICG-R15 is demonstrated to have a weak correlation to the histological staging of chronic hepatitis (Laennec's staging system) (20) while Child-Pugh A class has an insignificant correlation to Ishak fibrosis scoring system (8).

ICG-R15 is shown to be associated with PHLF (21-24) and is used to guide the extent of hepatectomies (11) but some researches show that ICG-R15 is not an independent factor in predicting of PHLF (6).

ICG clearance test helps surgeons to predict the histological fibrosis stage in order to make a safe decision of hepatectomies, especially major hepatectomies (over 3 segmentectomies). Therefore, we carry out this study to compare ICG clearance test and Child-Pugh score in evaluating of histological fibrosis stage (Ishak fibrosis staging system) and predicting of PHLF as well as create the model of staging estimation for fibrosis from liver function tests.

2. MATERIALS AND METHOD

2.1. Patients

This was a prospective cohort study from October 2016 to March 2021 at University Medical Center - Ho Chi Minh city. This article was one of the results of the research "The role of Indocyanine green test in evaluation of pre-hepatectomy liver function" which was accepted and allowed by the Ethical Board of Biomedical research of University of Medicine and Pharmacy at Ho Chi Minh city on July 9th 2019, ID 316/ĐHYD-HĐĐĐ.

All patients with ICG clearance test results before hepatectomies for malignant or benign liver tumors or donor, were included in the study. We excluded those with bile obstruction or chemotherapy within 1 month because these conditions render ICG clearance test results inaccurate (25, 26). This study included 340 patients.

2.2. Data collection

All patients' demographic data (gender, age), status of hepatitis, liver function tests (international normalized ratio of prothrombin time (INR), total serum bilirubin, serum albumin (Child-Pugh score)) and the platelet count (PLT) were collected. Pre-hepatectomy ICG clearance test was performed in all patients by LiMON method. After intravenous injection of indocyanine green 0.5 mg/kg, the indocyanine green disappearance rate was calculated by linear regression from the plasma concentrations of indocyanine green at 5, 10, and 15 minutes that gave us the two results: plasma disappearance rate (ICG-PDR) and ICG retention rate at 15 minutes (ICG-R15).

The operative factors (operation time, estimated blood loss, operative procedure) and the post-operative factors (histological staging of chronic hepatitis, tumor characteristics), liver function tests at post-operative day 3, 5, 7 (for PHLF diagnosis and grading), morbidity, mortality and hospital stay were recorded.

Histological staging of chronic hepatitis was based on Ishak fibrosis staging system for post-hepatectomy liver parenchyma (Ishak score) (27, 28).

PHLF was diagnosed and graded by International Study Group of Liver Surgery (ISGLS) criteria. PHLF is defined 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 INR and concomitant hyperbilirubinemia on or after postoperative day 5 (29).

Child-Pugh score was calculated by 2 clinical features (ascites, hepatic encephalopathy) and 3 blood tests (serum albumin, serum bilirubin, INR). This score and ICG clearance were analyzed and compared in relation to histological fibrosis stage and PHLF.

2.3. Statistical analysis

Data was analyzed by IBM SPSS 26.0 and R 4.0.5. Continuous variables were described by quartiles and were compared by T-test and One-Way ANOVA (standard distribution) or Mann-Whitney U test and Kruskal-Wallis test (non-standard distribution). Nominal or ordinal variables were described by incidence and compared by Chi-Square test or Fisher's Exact test.

Model of fibrosis staging was constructed based on ordinal logistic regression model, from univariate to multivariate model and reduced by backward stepwise variable selection based on AIC (Akaike Information Criterion). The index of effectiveness of the model was validated and optimism corrected by 1000-time bootstrap resampling.

3. RESULTS

3.1. Patient characteristics

There were 340 patients including 279 men (82.1%) and 61 women (17.9%). The patients' characteristics were shown in Table 1 and Table 2.

Table 1. Pre-operative characteristics (n = 340)

Characteristics	Median (Q1-Q3)/Number (%)
Age	59 (51 - 66)
BSA	1.66 (1.56 - 1.75)
Serum albumin (g/L)	40.60 (37.80 - 42.90)
Serum bilirubin (mmol/L)	12.20 (9.50 - 14.74)
INR	1.05 (1.00 - 1.11)
Platelet count (G/L)	214 (164 - 275)
ICG-PDR (%)	19.50 (16.60 - 22.70)
ICG-R15 (%)	5.40 (3.30 - 8.30)
Hepatitis	
Non-B non-C	82 (24.1)
B	206 (60.6)
C	51 (15.0)
B and C	1 (0.3)

Table 1. (continue)

Characteristics	Median (Q1-Q3)/Number (%)
Child-Pugh score	
5	306 (90.0)
6	31 (9.1)
7	3 (0.9)
Number of TACE	
No	273 (80.3)
1 time	50 (14.7)
2 times	7 (2.1)
≥ 3 times	10 (2.9)
Liver hypertrophy	
None	300 (88.2)
PVE (26 with previous TACE)	32 (9.4)
1st phase ALPPS (1 with previous TACE)	8 (2.4)

BSA: body surface area. INR: international normalized ratio. ICG-PDR: ICG plasma disappearance rate. ICG-R15: ICG retention rate at 15 minutes. TACE: transcatheter arterial chemoembolization. PVE: portal vein embolization. ALPPS: associating liver partition and portal vein ligation for staged hepatectomy

Table 2. Operative and post-operative characteristics (n = 340)

Characteristics	Median (Q1-Q3)/Number (%)
Operative time (minutes)	150 (120 - 180)
Blood loss (mL)	150 (100 - 200)
Hospital stay (days)	8 (7 - 10)
Hepatectomy	
Major (≥ 4 segments)	137 (40.3)
Minor (< 4 segments)	203 (59.7)
Morbidity	
No	268 (78.8)
PHLF	42 (12.4)
Other	30 (8.8)
PHLF	
No	298 (87.6)
Grade A	30 (8.8)
Grade B	10 (2.9)
Grade C	2 (0.6)
Death	3 (0.9)
Tumor nature	
HCC	270 (79.4)
Necrotic tissue (after TACE)	2 (0.6)
CCC	29 (8.5)
HCC + CCC	1 (0.3)
Liver metastasis	14 (4.0)
Neuroendocrine tumor	1 (0.3)
Benign tumor	14 (4.0)
Normal liver parenchyma (liver donation)	9 (2.7)
Histological fibrosis stage (Ishak score)	
0/6	112 (32.9)
1/6	53 (15.6)
2/6	33 (9.7)
3/6	54 (15.9)
4/6	46 (13.5)
5/6	36 (10.6)
6/6	6 (1.8)

PHLF: post-hepatectomy liver failure. HCC: hepatocellular carcinoma. CCC: cholangiocellular carcinoma. TACE: transcatheter arterial chemoembolization. Other morbidity included biliary fistula, ascites, fluid collection, biliary stenosis, intraoperative biliary injury, pneumonia, acute renal injury, myocardial infraction

3.2. Comparison of ICG clearance test and Child-Pugh score in histological fibrosis stage evaluation

There was no significant difference of Ishak score between men and women (p = 0.148). Age had a weak correlation to Ishak score with Spearman's rho of 0.167 significantly different from 0 (p = 0.002).

There were 80 patients with previous methods of treatment for liver hypertrophy before major hepatectomies including transcatheter arterial chemoembolization (TACE), portal vein embolization (PVE) (or both) or the 1st phase of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). These did not affect ICG-R15 (p = 0.141) and ICG-PDR (p = 0.138) as well as Ishak score (p = 0.074).

ICG-R15 had a weak correlation to Ishak score with Spearman's rho of 0.232 significantly different to 0 (p < 0.001) (Table 3).

Table 3. Relationship between pre-operative characteristics and histological fibrosis stage (Ishak score)

Characteristics	Spearman's rho	p
Gender		0.148
Age	0.167	0.002
Previous treatments		0.074
ICG-R15	0.232	< 0.001
Child-Pugh		0.257
Serum albumin	-0.087	0.121
Serum bilirubin	0.104	0.061
INR	0.156	0.004
Platelet count	-0.378	< 0.001

ICG-R15: ICG retention rate at 15 minutes. INR: international normalized ratio

There was no significant difference of Ishak score among 3 scores of Child-Pugh 5, 6, 7 (p = 0.257). Serum albumin and bilirubin had no correlation to Ishak score with Spearman's rho of -0.087 (p = 0.121) and 0.104 (p = 0.061) respectively, while INR had a weak correlation to Ishak score with Spearman's rho of 0.156 significantly different to 0 (p = 0.004).

Platelet count had a weak negative correlation to Ishak score with Spearman's rho of -0.378, significantly different to 0 (p < 0.001).

3.3. Model of histological fibrosis stage estimation

Based on the demographical variables (gender, age) and pre-operative liver function tests (ICG-R15, serum bilirubin, INR, platelet count), three models for histological staging estimation for fibrosis were constructed using the ordinal logistic regression model:

- Model 1: univariate of ICG-R15

- Model 2: multivariate of 6 upper variables

- Model 3: multivariate of 6 upper variables but reduced by backward stepwise variable selection based on Akaike Information Criterion (AIC)

Table 4 showed estimated parameters from these models and effectiveness in Ishak score estimation. ICG-R15, INR and female had a positive correlation to Ishak score (OR > 1, p < 0.05) while PLT and serum bilirubin had a negative

correlation to Ishak score (OR < 1, p > 0.05). PLT and serum bilirubin were not chosen in the reduced multivariate model. The index of effectiveness of the model was validated and optimism corrected by 1000-time bootstrap resampling.

Table 4. Model of histological fibrosis staging estimation

	Univariate		Multivariate		Reduced multivariate	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
ICG-R15 (double increase)	3.73 (2.11-6.57)	<0.001	1.36 (1.12-1.65)	0.001	2.75 (1.47-5.14)	0.001
Age (+1 year)	-	-	1.03 (1.01-1.04)	0.005	1.02 (1.00-1.04)	0.015
Sex: (Female to Male)	-	-	1.89 (1.00-2.93)	0.019	1.65 (0.97-2.81)	0.066
PLT (+10 G/L)	-	-	0.92 (0.89-0.94)	<0.001	0.92 (0.89-0.94)	<0.001
Serum bilirubin (+10 mmol/L))	-	-	0.89 (0.59-1.34)	0.677	-	-
INR (+0.1)	-	-	1.23 (0.97-1.56)	0.075	-	-
Effectiveness (AUC)	**0.59**		**0.68**		**0.68**	

OR: odd ratio for higher Ishak score when variables increase one unit or compare to standard value. CI: confidence interval. ICG-R15: ICG retention rate at 15 minutes. PLT: platelet count. INR: International Normolized Ratio. AUC: area under the curve

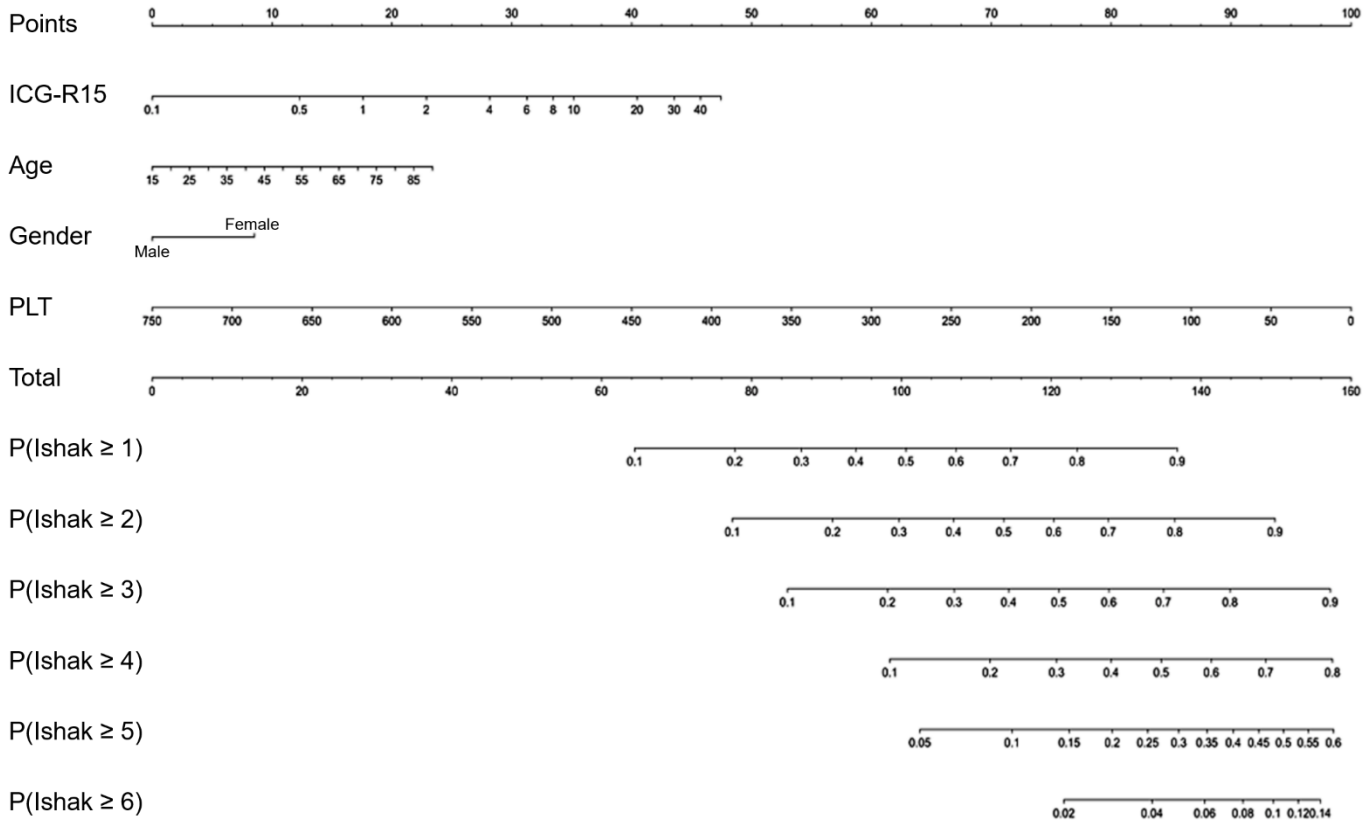

Figure 1. Nomogram for estimating of Ishak score

Table 5. Parameters from the reduced model

Parameters	Values
α_1 (to estimate P(Ishak ≥ 1))	0.73241
α_2 (to estimate P(Ishak ≥ 2))	-0.05656
α_3 (to estimate P(Ishak ≥ 3))	-0.50158
α_4 (to estimate P(Ishak ≥ 4))	-1.34980
α_5 (to estimate P(Ishak ≥ 5))	-2.35889
α_6 (to estimate P(Ishak ≥ 6))	-4.44481
β_1	1.01106
β_2	0.02192
β_3	0.50060
β_4	-0.08498

The effectiveness of each model shows that the multivariate analysis produced more accurate estimation than the univariate one. In spite of having less than 2 variables, the reduced multivariate model still produced the equivalent effectiveness to the full multivariate one. Between two patients with different Ishak score, the reduced multivariate model could identify the patient with the higher score with 69% accuracy.

In clinical practice, the estimating equation for Ishak score from the parameters in Table 5 or the simplified nomogram from the model could be used (Figure 1).

These steps could be followed to calculate the probability of Ishak score: (1) use the parameters in Table 5 and the value of ICG-R15, age, gender (Female = 1, Male = 0), PLT to

calculate the 6 probabilities of Ishak score ≥ n from following equation, (2) combine the 6 probabilities and clinical experience to decide the histological fibrosis stage of the patients.

$P(Ishak \geq n) = plogis(\alpha_n + \beta_1 \times log2(ICG\text{-}R15) + \beta_2 \times Age + \beta_3 \times Gender + \beta_4 \times (PLT/10))$

The process of calculation could be simplified as follows: (1) calculate the points of every variable based on the values of ICG-R15, age, gender, PLT, then calculate the total points, (2) calculate the 6 probabilities P (Ishak ≥ n) and combine them with clinical experience to decide the histological fibrosis stage of the patients.

3.4. Comparison of ICG clearance test and Child-Pugh score in predicting of PHLF

ICG clearance significantly was associated with PHLF (p = 0.019). ICG-R15 value in non-PHLF group is 0.75 times lower than PHLF-group (95% CI: 0.56 - 0.99). However, ICG-R15 was not associated with PHLF grading (Table 6).

Child-Pugh score was not associated with PHLF (p = 1.000). Component tests of Child-Pugh score (including serum albumin, serum bilirubin, INR) and platelet count were not associated with PHLF significantly (p = 0.108, 0.136, 0.864, 0.296 respectively).

Table 6. Relationship between liver function tests and PHLF

	Non-PHLF (n= 298)	PHLF (n = 42)	p
ICG-R15 (%)	5.20 (3.10 - 8.23)	6.20 (4.25 - 9.53)	**0.039**
Serum albumin (g/L)	40.60 (37.95 - 42.98)	39.10 (36.40 - 41.58)	0.108
Serum bilirubin (mmol/L)	12.20 (9.50 - 14.67)	12.62 (9.45 - 18.98)	0.136
INR	1.05 (1.00 - 1.12)	1.06 (0.99 - 1.11)	0.864
Platelet count (G/L)	214 (165 - 278)	216 (129 - 266)	0.296

Statistics are median (Q1-Q3); PHLF: post-hepatectomy liver failure. ICG-R15: ICG retention rate at 15 minutes. INR: international normalized ratio

4. DISCUSSION

ICG-R15 is the most useful test for Asia - Pacific surgeons to evaluate pre-hepatectomy liver function and guide the majority of hepatectomies (9, 11) as well as predict PHLF (6, 21-24, 30). In this study, the median value of ICG-R15 was 5.4% (3.3 - 8.3%) which was good and common for hepatectomy.

The analysis of 80 patients with preceding treatments before hepatectomy, such as TACE or PVE or 1st phase ALPPS, showed that these treatments did not affect ICG-R15 and Ishak score and therefore, these did not affect analysis of the correlation of these two variables.

ICG-R15 had a weak correlation with Ishak score (r = 0.232) which corresponded another research using Laennec's histological staging of chronic hepatitis system among Child-Pugh A patients with r = 0.325 (20). Although the correlation coefficient was low, surgeons still had a useful tool to estimate the histological fibrosis stage before hepatectomy. Child-Pugh score did not significantly relate to the Ishak fibrosis stage which concurred our hospital's previous study (8). This might result from the fact that most of the patients in this study had Child-Pugh class A. This proved that good Child-Pugh score did not mean good liver parenchyma, which made it difficult for surgeons to make decisions of hepatectomy. Therefore, ICG clearance test was more valuable than Child-Pugh score in evaluation of histological fibrosis stage among patients indicated for hepatectomies. However, ICG-R15 was weaker than platelet count and stronger than INR in the correlation with Ishak score. This suggests that there was no best single test to predict the histological fibrosis stage, hence, the model of histological staging estimation for fibrosis was constructed.

The model was set up based on variables from the general knowledge and clinical experience of the relationship between cirrhosis and ICG-R15, age, gender, serum bilirubin, INR, platelet count. Ishak score was the ordinal variable (based on the histological staging); therefore, we could not estimate the score directly based on calculating but just on the probabilities of every stage. Surgeons should combine the probabilities of stages and clinical experience to decide which stage is suitable for the patient. Although the accuracy of this model was quite low, at 68%, it was already useful for surgeons to determine the indication and the extent of liver resection because it enabled the prediction of histological fibrosis stage for approximately 2/3 patients of hepatectomies.

As regards post-operative results, ICG-R15 in non-PHLF group was 0.75 times lower than PHLF group. In the absolute value of ICG-R15, this was not the large gap, but the difference of 25% was significantly notable. However, ICG-R15 did not significantly relate to PHLF grading. It is presumably because the quantities of PHLF grade B-C is low in this study. So, this study could not demonstrate the role of ICG-R15 in prognosticating the severity of PHLF. There was no evidence that Child-Pugh score and component tests as well as platelet count relate to the PHLF and its grades. In summary, ICG-R15 was better than Child-Pugh score in predicting of PHLF. This finding was similar to the result of Wang et al (24) which demonstrated that ICG-R15 was better than Child-Pugh score in prediction of PHLF.

This study had a quite large sample of 340 patients with all stages of histological fibrosis and cirrhosis and all kinds of hepatectomy which made the results more reliable and able to apply to clinical practice. Besides, this is one of very few studies about the relationship between liver function tests and histological fibrosis stage. However, comparing the continuous variable (ICG-R15) and the ordinal variable (Child-Pugh score) in correlation with another ordinal variable (Ishak score) was very challenging. Based on the clinical experience, we separated the component tests Child-Pugh scoring system and added platelet count to analyze the correlation to Ishak score to clarify the roles of the traditional liver function tests with the new one. In spite of this limitation, we still hoped this study would help surgeons have more information about pre-hepatectomy liver function assessments.

Conclusion

ICG clearance test, through ICG-R15 had a weak correlation to Ishak fibrosing score with r = 0.232. Child-Pugh score did not significantly correlate to Ishak fibrosing score while platelet count had a weak negative correlation with r = -0.378. It was possible to estimate the Ishak fibrosing score based on gender, age, ICG-R15 and platelet count with the accuracy 68%. ICG clearance test was also better than Child-Pugh (and component tests) in predicting of PHLF.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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