Value of Preoperative Indocyanine Green Clearance Test for Predicting Post-Hepatectomy Liver Failure in Noncirrhotic Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 **Cem Ibis**
AB 2 **Dogan Albayrak**
CDE 3 **Tayfun Sahiner**
B 1 **Yigit Soytas**
CD 4 **Basak Gurtekin**
BD 5 **Nukhet Sivrikoz**

1 Department of General Surgery, Division of Hepato-Pancreato-Biliary (HPB) Surgery and Liver Transplantation, Istanbul University Medical Faculty, Istanbul, Turkey
2 Department of General Surgery, Trakya University Medical Faculty, Edirne, Turkey
3 Department of General Surgery, Hitit University Medical Faculty, Corum, Turkey
4 Department of Biostatistics, Istanbul University Istanbul Medical Faculty, Istanbul, Turkey
5 Department of Anesthesiology and Reanimation, Istanbul University Istanbul Medical Faculty, Istanbul, Turkey

Corresponding Author: Cem Ibis, e-mail: acemibis@hotmail.com
Source of support: Departmental sources

Background: Liver failure is the most feared complication following hepatectomy. Post-hepatectomy liver failure (PHLF) is closely related to the remnant liver volume, and functional reserve. There are several methods for predicting PHLF prior to liver resection. The indocyanine green (ICG) clearance test was popularized in patients with hepatocellular cancer (HCC). We aim to demonstrate the value of preoperative ICG clearance measurement via pulse spectrophotometer (LIMON®) in prediction of PHLF in noncirrhotic patients prior to liver resection.

Material/Methods: Fifty-three noncirrhotic patients who underwent liver resection due to different pathologies were included. Retrospectively collected clinical data, including the preoperative ICG clearance measurements and remnant liver volumes of the patients, were statistically evaluated according to the PHLF criteria of the International Study Group of Liver Surgery.

Results: Four (7.5%) patients with PHLF were observed. There was no significant difference between PHLF and non-PHLF groups regarding ICG clearance measurements with cut-off values of 5% and 9.5%.

Conclusions: The ICG clearance test does not satisfy our expectations in noncirrhotic patients in predicting PHLF. We believe that the ICG clearance test should be reserved for patients with cirrhosis and/or HCC. This test could be an option for noncirrhotic patients with chronic active hepatitis, advanced-grade fatty livers, or for patients who received long-term preoperative chemotherapy, and also for patients who underwent single or multiple sessions of TACE or TARE prior to liver resection. If the routine selection criteria have been fulfilled, there is no further need to perform the ICG clearance test for living liver donors.

MeSH Keywords: Hepatectomy • Indocyanine Green • Liver FailureX

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/907306

📄 3229   🖼 4   📊 —   📚 21

Background

Liver failure is the most feared complication following hepatectomy [1]. Post-hepatectomy liver failure (PHLF) is closely related to the remnant liver volume, and functional reserve. There are several methods for predicting PHLF prior to liver resection [1]. Assessing the future liver remnant volume (FLRV) as a critical parameter is the *sine qua non* for a safe hepatectomy. In addition to remnant liver volume (RLV) calculation and static liver function tests, dynamic tests such as indocyanine green clearance (ICG_{R15}), galactose elimination capacity, and methacetin breath test (liver maximum capacity) are widely used by different groups according to their preferences [1,2]. The ICG_{R15} test was introduced and popularized by Makuuchi et al. in the 1980s, especially in patients with hepatocellular cancer (HCC) [1]. The ICG_{R15} test became a standard preoperative parameter in cirrhotic patients prior to hepatectomy, mostly in Asian series. With the development of noninvasive pulse spectrophotometers for measurement of ICG_{R15}, rapid assessment of liver function is possible prior to hepatectomy in patients with liver failure as well as in patients with sepsis in intensive care units and in patients with acute hepatitis, hepatosteatosis, or receiving chemotherapy [3]. In our clinic, we integrated the ICG_{R15} test into the routine preoperative evaluation of hepatectomy candidates, including living donors for liver transplantation. In addition to patients with chronic liver disease, data were also accumulated about patients without cirrhosis before and after the planned hepatectomy. We designed the present retrospective study to demonstrate the value of preoperative ICG_{R15} measurement in prediction of PHLF in noncirrhotic patients prior to liver resection.

Material and Methods

Our retrospective observational study included 53 noncirrhotic (all histologically-proven) patients who underwent hepatectomy between 2012 and 2016 in the Department of Hepatobiliary Surgery and Liver Transplantation of the Istanbul School of Medicine, Istanbul University. Patients with chronic liver disease, whose follow-up period was shorter than 6 months, or with lacking data, were excluded. We collected data on sex, age, height, weight, diagnosis, comorbidity, smoking history, alcohol consumption, preoperative systemic chemotherapy, surgical procedure, preoperative-early postoperative (1-day), and late postoperative (5-day) laboratory values, including platelet (PLT) count, lactate dehydrogenase (LDH), creatinine (CREA), alanine aminotransaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), international normalized ratio (INR), C-reactive protein (CRP), intraoperative total inflow occlusion time (intermittent [15/5 minutes] type Pringle's maneuver; whereas inflow occlusion

maneuver was not used in liver donors), intraoperative hemoglobin (Hb) decrease (as the sign of intraoperative hemorrhage), length of postoperative hospitalization, postoperative complications according to Clavien-Dindo classification, and mortality rates (in-hospital, 30-, 90-, and 120-day). Body-mass index (BMI), body surface area (BSA) according to DuBois formula, and total liver volume (TLV) according to the formula of Vauthey et al. [4,5] were calculated.

Indocyanine Green Clearance (ICG_{R15}) test

Prior to liver resection, 0.5 mg/kg of indocyanine green (ICG) (ICG-PULSION Medical Systems, Germany) was injected into a peripheral vein of the patient (with TBIL level <2mg/dl and normal oxygen saturation) and 15-min retention rate of ICG was the measured using a pulse spectrophotometer (LIMON®; Pulsion Medical Systems, Munich, Germany). ICG retention rate ($ICG_{R15LIMON}$) and ICG plasma disappearance rate (PDR) were noted. The LIMON measurements were converted to conventional spectrophotometric ICG retention rates ($ICG_{R15SPECTRO}$) using the Purcell formula [3,6].

Using computed tomography (CT) software (ExtremePACS 2016 Ankara, Turkey, licensed to Istanbul University), FLRV and planned liver resection rates were calculated from the abdominal CT scans.

Although there are still many different definitions of PHLF, we decided to use the criteria developed by the International Study Group of Liver Surgery (ISGLS) for PHLF (increased INR and hyperbilirubinemia according to the normal cut-off levels defined by the local laboratory on or after postoperative day 5) [7,8]. According to ISGLS-PHLF criteria, we established 2 different groups among the patients in our study: PHLF and non-PHLF.

Our series included 20 liver donors who had "healthy" livers prior to the hepatectomy operation. In addition to the initial grouping, we divided the patients into 2 different groups: liver donors as "healthy controls" and other patients with different liver diseases. An extra comparison of PHLF between these groups was also made.

Statistical analysis

All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA, Licensed to Istanbul University) statistical software. The appropriateness of continuous variables for normal distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous variables were compared using parametric tests and continuous variables without normal distribution were compared using non-parametric statistical tests. Continuous variables are expressed as median (range). Categorical variables were compared using

the chi-square test and Fisher's exact test, as appropriate. The correlation between the TLV, $ICG_{R15LIMON}$, and $ICG_{R15SPECTRO}$ was evaluated using Spearman analysis. Continuous variables were compared using the independent samples t test or Mann-Whitney U test. A p value <0.05 was considered statistically significant. Statistical evaluation of the relationship between the diagnosis of PHLF and $ICG_{R15LIMON}$, and $ICG_{R15SPECTRO}$ was performed through sensitivity, specificity, positive predictive value, negative predictive value, and the accuracy calculation according to different cut-off levels.

Results

A total of 53 patients (26 [49%] females and 27 [51%] males) were included into our study. The median age was 45 years (range, 19 to 76). We established PHLF and non-PHLF groups using TBIL and INR values on the 5th postoperative day according to the ISGLS-PHLF criteria. The PHLF group consisted of 4 (7.5%) patients; 3 patients (75%) out of 4 had grade B PHLF and the remaining 1 patient developed grade A PHLF. No grade C PHLF according to ISGLS criteria was observed.

The median BMI was 24.2 kg/m^2 (range, 17.95 to 33.70). Median height was 169 cm (range, 136 to 195), and the median weight was 71 kg (range, 50 to 101). Median BSA was calculated as 1.78 m^2 (range, 1.36 to 2.18).

There was no statistically significant difference in terms of sex, age, BMI, height, weight, and BSA between PHLF and non-PHLF groups (Table 1).

In 28 patients (53%), the cause of liver resection were malignant diseases and the remaining 47% of the patients had benign disorders (Table 2). The comparison between PHLF and non-PHLF groups did not show any significant difference regarding diagnoses prior to liver resection. Thirty-nine (73%) patients had at least 1 comorbid disease. No alcohol consumption was reported by 98% of patients and no smoking was reported by 86% of the patients. In the preoperative period, 8 patients (15.1%) received chemotherapy, 1 patient (1.8%) underwent transarterial radioembolization (TARE), 1 patient (1.8%) underwent transarterial chemoembolization (TACE), and 1 patient (1.8%) underwent portal vein embolization (PVE). Although the viral serology was negative in 48 patients (90.6%), 3 patients (5.7%) had hepatitis B surface antigen and 2 patients (3.8%) had positive hepatitis C serology. Surgical procedures are summarized in Table 3. Statistical evaluation did not reveal any significant difference between PHLF and non-PHLF groups in terms of comorbid diseases, alcohol consumption history, smoking habits, positive viral serology, or preoperative chemotherapy history. Preoperative DBIL, ALP, AST, GGT, and CRP levels were found to be significantly different between PHLF

and non-PHLF groups. The median total duration of inflow occlusion was 23.4 minutes (range, 0 to 65). The comparison of the PHLF and non-PHLF groups regarding the total duration of Pringle's maneuver did not show significant difference. The median Hb decrease during the liver resection was 1.4 g/dl (range, 0 to 4.5). No significant difference was detected between groups concerning Hb decrease. Median postoperative hospitalization was 10 days (range, 6 to 55) and no significant difference was found between groups. According to Clavien-Dindo classification, a total of 15 patients (28%) developed postoperative complications (8 [15%] patients were grade I, 6 [11%] were grade II, and 1 [1.8%] were grade III). A statistically significant difference was found between PHLF and non-PHLF groups in terms of postoperative complications (p=0.002).

The 30-, 90-, 120-day, and overall mortality rates were 0%, 1.8%, 3.8%, and 3.8%, respectively. The only in-hospital mortality occurred on the 49th postoperative day. There was no significant difference between groups regarding mortality (p=0.147). The median preoperative TLV was 1470 cm^3 (range, 929 to 1968) and the preoperative median PLT count was 233000/mm^3 (range, 70 100 to 494 000). No significant difference was found between groups regarding preoperative TLV and PLT count [Table 4].

Median $ICG_{R15LIMON}$ was 2% (range, 0.1 to 18.4), median PDR was 26%/minute (range, 11.3 to 48.9). The calculated $ICG_{R15SPECTRO}$ had a median value of 5.25% (range, 3.54 to 20.97). There was no significant difference between PHLF and non-PHLF groups in terms of $ICGR_{15LIMON}$, PDR, and $ICG_{R15SPECTRO}$ values.

Different cut-off levels of $ICG_{R15LIMON}$ and $ICG_{R15SPECTRO}$ were selected in order to examine the predictive value of indocyanine green retention rates. The sensitivity (SEN), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) of $ICG_{R15LIMON}$ greater than or equal to 9.5% for the prediction of PHLF in noncirrhotic patients were 25%, 93.8%, 25%, 93.8%, and 88.7%, respectively. SEN, SPE, PPV, NPV, and ACC of $ICG_{15LIMON}$ greater than or equal to 5% for the prediction of PHLF were 25%, 83.7%, 11.1%, 93.2%, and 79.2%, respectively. No statistically significant difference was detected between PHLF and non-PHLF with cut-off levels of 5% and 9.5% for $ICG_{R15LIMON}$ measurements (p=0.276 and p=0.536, respectively). SEN, SPE, PPV, NPV, and ACC of $ICG_{15SPECTRO}$ greater than or equal to 15% for the prediction of PHLF were 25%, 98%, 50%, 94.1%, and 92.5%, respectively. SEN, SPE, PPV, NPV, and ACC of $ICGR_{15SPECTRO}$ greater than or equal to 10% for the prediction of PHLF were 25%, 93.9%, 25%, 93.9%, and 88.7%, respectively. No statistically significant difference was detected between PHLF and non-PHLF with cut-off levels of 10% and 15% for $ICG_{R15SPECTRO}$ values (p=0.147 and p=0.276, respectively).

Table 1. Characteristics of all patients in the study.

	non-PHLF		PHLF		
Age	45	(19–72)	57	(49–76)	p=0.053
Sex (Male: Female)	25: 24		2: 2		n.s.
BMI %	24	(17–33)	26	(20–27)	p=0.919
BSA m^2	1.79	(1.36–2.18)	1.69	(1.58–1.98)	p=0.400
TLV ml	1474	(929–1968)	1347	(1207–1714)	p=0.400
ICG$_{R15LIMON}$ %	1.9	(0.1–13.4)	4.1	(1.2–18.4)	p=0.157
PDR %/min	26.5	(13.4–48.9)	21.4	(11.3–29.5)	p=0.178
ICGR$_{15SPECTRO}$ %	5.16	(3.53–16.68)	21.4	(11.3–29.5)	p=0.138
Preop LDH IU/l	290	(72–1186)	282	(179–798)	p=0.893
Preop CREA mg/dl	0.8	(0.5–1.10)	0.8	(0.5–1.00)	p=0.865
Preop TBIL mg/dl	0.45	(0.21–2.07)	0.65	(0.52–0.73)	p=0.157
Preop DBIL mg/dl	0.16	(0.06–1.88)	0.34	(0.26–0.36)	p=0.015
ALP IU/l	76	(39–358)	203	(92–533)	p=0.018
AST IU/l	20	(10–220)	33	(26–42)	p=0.049
ALT IU/l	18	(6–83)	32	(24–35)	p=0.125
GGT U/l	17	(70–778)	186	(92–315)	P=0.004
INR	1.03	(0.89–1.33)	1.11	(0.96–1.28)	P=0.244
CRP mg/dl	2.18	(0.03–36)	18.04	(3.06–42.76)	p=0.014
PLT ×10^3/mm^3	233	(106–494)	220	(70.1–310)	p=0.511
Disease Benign: Malign	23: 26		0: 4		p=0.490
Comorbidity (+/–)	13/36		1/3		p=0.896
Viral serology (+/–)	5/44		0/4		p=0.502
Status Exitus: Alive	1: 48		1: 3 p=0.147		
Pringle time minutes	30	(0–65)	32	(22–45)	p=1.000
Remnant liver rate %	46	(21–99)	55	(42–86)	p=0.469
Hb decrease g/dl	1.33	(0–4)	2.35	(0.6–4.5)	n.s.

Median values (range).
PHLF – Posthepatectomy liver failure; n.s. – not significant; BMI – body mass index; BSA – body surface area; TLV – total liver volume; ICG$_{R15LIMON}$ – indocyanine green clearance measured by pulse dye spectrophotometer; ICG$_{R15SPECTRO}$ – indocyanine green clearance value converted to spectrophotometer reading; PDR – indocyanine plasma disappreance rate; LDH – lactate dehydrogenase; CREA – creatinine; ALT – alanin aminotransaminase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; GGT – gamma-glutamyltransferase; TBIL – total bilirubin; DBIL – direct bilirubin; INR – international normalized ratio; CRP – C-reactive protein; PLT – platelet count; Hb – hemoglobin.

Table 2. The diagnoses of the patients underwent liver resection.

Diagnose	Frequency	Percentage (%)
Colorectal cancer metastasis	15	28.3
Klatskin's tumor	7	13.2
Living liver donor	21	39.6
Hemangioendothelioma	1	1.9
Hepatocellular cancer	6	11.3
Hepatic adenoma	1	1.9
Alveolar hydatid disease	1	1.9
Hemangioma	1	1.9
Total	**53**	**100.0**

Table 3. Surgical Procedures.

Procedure	Frequency	Percent
Right hepatectomy	25	47.2
Left hepatectomy	6	11.3
Extended left hepatectomy	3	5.7
Extended right hepatectomy	6	11.3
Metastasectomy	3	5.7
Left lateral sectionectomy	6	11.3
Right posterior sectionectomy	2	3.8
Right trisectionectomy	2	3.8
Total	**53**	**100.0**

Table 4. The characteristics of patients with posthepatectomy liver dysfunction.

Patient No	1	2	3	4
PHLF Grade	A	B	B	B
Age years	51	76	49	62
Sex	Male	Male	Female	Female
Weight kg	80	60	66	62
BMI kg/m^2	25	20	27	27
Diagnosis	PHCC	Colon Cancer Met.	PHCC	Colon Cancer Met.
Surgical procedure	Right Hx + Caudate lobectomy+ Bile Duct Rx	Extended right Hx	Right Hx + Caudate lobectomy+ Bile Duct Rx+ Portal vein Rx &Reconst.	Right Hx+ VCI repair
Hb decrease g/dl	0.6	3	1.3	4.5
Pringle's M min	45	22	30	32
RLV ml	816	1118	626	1151
sFLR %	48	81	50	86
RLV %	43	42	48	95
ICG$_{R15LIMON}$ %	4.7	18.4	3.4	1.2
ICG$_{R15SPECTRO}$ %	7.9	20.9	6.7	4.6
PDR %	20.1	11.3	22.6	29.5
Comorbidity	Absent	Absent	Hypertension+ Asthma	Absent
Preoperative treatment	None	None	Chemotherapy+ TARE + TACE	None
Postoperative hospitalization days	13	27	30	17
Status	Alive	Died	Alive	Alive

PHLF – posthepatectomy liver failure; BMI – body mass index; PHCC – perihilar cholangiocarcinoma; Tm – tumor; Met – metastasis; Hx – hepatectomy; Rx – resection; VCI – vena cava inferior; Reconst – reconstruction; Hb – hemoglobin; M – maneuver; min – minutes; RLV – remnant liver volume; sFLR – stardatized future liver remnant; ICG$_{R15LIMON}$ – Indocyanine green clearance measured by pulse spectrophotometer; ICG$_{R15SPECTRO}$ – Indocyanine green clearance value converted to conventional spectrophotometer readings; PDR – Indocyanine plasma disappearnce rate; TARE – transarterial radioembolization; TACE – transarterial chemoembolization.

The median RLV was 697 ml (range, 303 to 1516) and the median rate of RLV was 46% (range, 21 to 99). There was no significant difference between PHLF and non-PHLF groups regarding RLV and the rates of RLV. The Spearman analysis did not show any correlation between TLV, $ICG_{R15LIMON}$, PDR, and $ICGR_{15SPECTRO}$ values (p=0.678, p=0.415, and p=0.617, respectively).

From a critical point of view, liver donors could be interpreted as a "healthy" group, so we decided to divide the series into 2 groups: a liver donors (LD) group and an "other hepatectomies" (OH) (liver resections due to tumoral causes) group. The LD group included 20 patients (10 males, 10 females) and the OH group included 33 patients (17 males, 16 females). No PHLF developed in the LD group. All of the 4 patients with PHLF were in the OH group. However, there was no significant difference between LD and OH groups in terms of PHLF (p=0.285). Although there was no significant difference regarding sex, alcohol consumption, smoking habits, viral serology, BSA, TLV, length of postoperative hospitalization, and postoperative complications between LD and OH groups, we found that median age, BMI, and $ICG_{R15LIMON}$ were significantly lower in the LD group (p=0.000, p=0.004, and p=0.034, respectively). In the LD group, median $ICG_{R15LIMON}$ was 1.6% (range, 0.1 to 5.5), and in the OH group $ICGR_{15LIMON}$ was 3.4% (range, 0.1 to 18.4). No significant difference was found between groups regarding PDR and $ICGR_{15SPECTRO}$ values. Preoperative LDH, ALP, AST, ALT, CREA, and CRP levels were also significantly lower in the LD group than in the OH group. No significant difference was detected between preoperative TBIL, DBIL, INR, and PLT values among groups. RLV was higher in the OH (median RLV=816 ml) group than in the LD (median RLV=529 ml) group (p=0.023).

We made an extra effort to make a subgroup analysis in our series of noncirrhotic patients, dealing only with hepatectomized patients and excluding the liver donors. Thus, we had a small subgroup of 33 patients (4 with PHLF and 29 non-PHLF). The analysis did not show statistically significant differences between PHLF and non-PHLF patients in terms of $ICGR_{15LIMON}$, PDR, and $ICGR_{15SPECTRO}$ values. Only 2 variables – preoperative chemotherapy and viral serology positivity – were significantly different among PHLF and non-PHLF patients (p=0.003 and p=0.023, respectively).

Discussion

PHLF is the most serious complication after hepatic resection. Preoperative calculation of FLRV and static liver function tests, as well as dynamic functional evaluation of liver through clearance, elimination, and metabolite formation tests, are used to predict PHLF [1,3]. Prediction of PHLF almost always leads to preventive interventions such as portal vein embolization and ligation, and biliary drainage procedures preoperatively to avoid PHLF, or even deciding not to perform a major resection and to proceed with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS procedure), which has recently become common practice [1].

Since liver resection is an effective surgical treatment for a broad variety of benign and malignant hepatic tumors, PHLF will stay on the agenda of HPB surgeons. Different groups have been trying to develop new strategies to improve liver regeneration capacity [9,10]. Due to the impaired liver function in patients with cirrhosis, the risk of PHLF cannot be assessed accurately by volumetric evaluation alone; therefore, ICG clearance test has been commonly used for many years in patients with cirrhosis before hepatectomy [11]. In addition to hepatocellular cancer (HCC) patients with or without cirrhosis, $ICG_{R15LIMON}$ and PDR measurements have also long been part of our routine clinical preoperative evaluation for all patients prior to liver resection near assessment of FLRV and liver function tests. Previous studies have reported PHLF incidence rates of 9.0% to 39.6% [12–14]. Retrospective evaluation of our series including noncirrhotic patients who underwent liver resection revealed that 7.5% of patients developed PHLF according to ISGLS criteria.

Although there are many different descriptions of and arguments about PHLF, the PHLF definition according to ISGLS is reliable and easy to use [7,15]. Despite our meticulous and detailed selection criteria (FLRV: body weight ≥0.6, TBIL ≤3 g/dl, FLRV >20%, and $ICG_{R15LIMON}$ <10%) for liver resection, we recognized 4 patients with grade A or B ISGLS-PHLF. Strict use of selection criteria would have probably prevented a PHLF of grade C. Although it was reported that high BMI values are associated with increased risk of PHLF, there was no significant difference between PHLF and non-PHLF groups regarding BMI values. Perhaps we could not find a correlation between BMI and PHLF because the highest BMI was 33.7 in our series. Similar to previous studies, age is not a risk factor for hepatectomy [16].

There are different reports about the effects of preoperative chemotherapy regarding PHLF [17]. We did not find any difference between patients with and without previous chemotherapy regarding PHLF. Some previous reports focused on hepatitis reactivation due to hepatectomy rather than viral serology positivity regarding PHLF [18]. There was no statistically significant difference between PHLF and non-PHLF groups in terms of hepatitis serology positivity. Although the preoperative DBIL, ALP, AST, GGT, and CRP levels were significantly higher in the PHLF group, the DBIL and AST values were within normal limits. The significance of the elevated values of ALP, GGT, and CRP among groups, which we could not determine exactly, could be a potential clue to help establish a prediction formula for PHLF in the future.

Although some authors reported that the preoperative PLT count is more useful than ICG clearance test for predicting PHLF in HCC patients, we did not observe this in our series of noncirrhotic patients [7]. Intraoperative events like bleeding and transfusion are independent risk factors for PHLF [1]. There was no significant difference between PHLF and non-PHLF groups regarding intraoperative Hb decrease and total Pringle's maneuver duration. Despite the fact that RLV is strongly associated with PHLF, there was no significant difference between PHLF and non-PHLF patients in terms of RLVs. This can be explained as the absence of patients with an RLV lower than 21% in our series.

As we also expected, postoperative complications were significantly more common in the PHLF group. The 30- and 120-day mortality rates in our series were 0% and 3.8%, respectively. None of our mortalities were PHLF-related. Large hepatectomy series including only noncirrhotic patients reported mortality rates between 0.8% and 7% [19].

Because we were unable to show any difference between PHLF and non-PHLF groups regarding $ICG_{R15LIMON}$ and $ICG_{R15SPECTRO}$, we decided to change the cut-off levels and analyze the outcome. Use of cut-off levels of 9.5% and 5% for $ICG_{R15LIMON}$ and cut-off values of 15% and 10% for $ICG_{R15SPECTRO}$ did not achieve satisfying and reliable PPV rates for PHLF. The ICG clearance test was unable to predict the PHLF preoperatively in noncirrhotic patients even after lowering the cut-off levels of ICG retention rates below the previously reported normal values.

Since there was no correlation between TLV, PDR, $ICG_{R15LIMON}$, and $ICG_{R15SPECTRO}$, we can conclude that TLV is not related with ICG clearance rates in noncirrhotic patients.

We did not find any differences between PHLF and non-PHLF groups in terms of benign and malignant diseases. However, we established 2 further subgroups – LD and OH – to compare liver donors ("healthy livers") with the other patients ("diseased livers"). There were no significant differences regarding the examined parameters except for median age, BMI, $ICG_{R15LIMON}$, preoperative LDH, ALP, AST, ALT, CREA, and INR, which were significantly lower (but within normal limits) in the LD group than in the OH group. This finding may support use of the term "diseased liver". In addition, RLVs in the LD group were significantly higher than in the OH group, probably due to our strict living liver donor selection criteria. We did not see any PHLF in the LD group, but some authors reported that PHLF arises in 8% of patients after hepatectomy in liver donors [20].

The statistical analysis of the newly-established group after excluding the liver donors showed only that PHLF was significantly more common in patients who received preoperative chemotherapy and had positive viral serology (hepatitis B, C, or both) than in patients with negative viral serology and without previous chemotherapy. Despite the optimal volume of remnant liver after hepatectomy and normal values of PDR, $ICG_{R15LIMON}$, and $ICG_{R15SPECTRO}$, PHLF developed in this small group of patients.

There are unfortunately some limitations of our study. Our small series of noncirrhotic patients included only a few cases with PHLF, which obviously limited our interpretations despite meticulous statistical evaluation. The large number of guides or criteria with alternative definitions of PHLF made it difficult to select the right method to determine liver failure of different grades. We should perhaps expand our noncirrhotic hepatectomy series by adding new predictive modalities for PHLF, like mebrofenin hepatobiliary scintigraphy, in future research [21].

Conclusions

ICG clearance test did not satisfy our expectations in noncirrhotic patients in predicting PHLF. We believe that the ICG clearance test should be reserved for patients with cirrhosis and/or HCC. This test could be an option for noncirrhotic patients with chronic active hepatitis, high grade hepatosteatosis, or for patients who received long-term preoperative chemotherapy, and also for patients who underwent single or multiple sessions of TACE or TARE prior to liver resection.

If the routine selection criteria have been fulfilled, there is no further need to perform the ICG clearance test for living liver donors. Hepatobiliary surgeons should take PHLF into account when performing a liver resection, even in patients who were meticulously selected for hepatectomy, and should consider using PVE liberally as a precaution against RLV. Recent trials dealing with mebrofenin hepatobiliary scintigraphy seem to be very promising in predicting PHLF.

Acknowledgements

Conflicts of interest

None.

References:

1. Karanicolas PJ: Assessment of hepatic function: Implications for the surgical patient. In: Jarnagin WR AP, Chapman WC, D'Angelica MI (eds.), Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 6 ed. Philadelphia: Elsevier, 2017; 61–65

2. Jara M, Reese T, Malinowski M et al: Reductions in post-hepatectomy liver failure and related mortality after implementation of the LiMAx algorithm in preoperative work-up: A single-centre analysis of 1170 hepatectomies of one or more segments. HPB (Oxford), 2015; 17(7): 651–58

3. De Gasperi A, Mazza E, Prosperi M: Indocyanine green kinetics to assess liver function: Ready for a clinical dynamic assessment in major liver surgery? World J Hepatol, 2016; 8(7): 355–67

4. Um EH, Hwang S, Song GW et al: Calculation of standard liver volume in Korean adults with analysis of confounding variables. Korean J Hepatobiliary Pancreat Surg, 2015; 19(4): 133–38

5. Ribero D, Zimmitti G, Aloia TA et al: Preoperative cholangitis and future liver remnant volume determine the risk of liver failure in patients undergoing resection for hilar cholangiocarcinoma. J Am Coll Surg, 2016; 223(1): 87–97

6. Cheung TT, Chan SC, Chok KS et al: Rapid measurement of indocyanine green retention by pulse spectrophotometry: A validation study in 70 patients with Child-Pugh A cirrhosis before hepatectomy for hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int, 2012; 11(3): 267–71

7. Fukushima K, Fukumoto T, Kuramitsu K et al: Assessment of ISGLS definition of posthepatectomy liver failure and its effect on outcome in patients with hepatocellular carcinoma. J Gastrointest Surg, 2014; 18(4): 729–36

8. Rahbari NN, Garden OJ, Padbury R et al: Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery, 2011; 149(5): 713–24

9. Cai T, Deng Q, Zhang S et al: Peripheral blood stem cell transplantation improves liver functional reserve. Med Sci Monit, 2015; 21: 1381–86

10. Kuroda S, Tashiro H, Kobayashi T et al: Administration of antithrombin III attenuates posthepatectomy liver failure in hepatocellular carcinoma. Dig Surg, 2015; 32(3): 173–80

11. Kim HJ, Kim CY, Park EK et al: Volumetric analysis and indocyanine green retention rate at 15 min as predictors of post-hepatectomy liver failure. HPB (Oxford), 2015; 17(2): 159–67

12. Uchida Y, Furuyama H, Yasukawa D et al: Hepatectomy based on future liver remnant plasma clearance rate of indocyanine green. HPB Surg, 2016; 2016: 7637838

13. Tomimaru Y, Eguchi H, Gotoh K et al: Platelet count is more useful for predicting posthepatectomy liver failure at surgery for hepatocellular carcinoma than indocyanine green clearance test. J Surg Oncol, 2016; 113(5): 565–69

14. Iguchi K, Hatano E, Yamanaka K et al: Validation of the conventional resection criteria in patients with hepatocellular carcinoma in terms of the incidence of posthepatectomy liver failure and long-term prognosis. Dig Surg, 2015; 32(5): 344–51

15. Skrzypczyk C, Truant S, Duhamel A et al: Relevance of the ISGLS definition of posthepatectomy liver failure in early prediction of poor outcome after liver resection: study on 680 hepatectomies. Ann Surg, 2014; 260(5): 865–70; discussion 870

16. Lodewick TM, Alizai PH, van Dam RM et al: Effect of age on liver function in patients undergoing partial hepatectomy. Dig Surg, 2017; 34(3): 233–40

17. Volk AM, Fritzmann J, Reissfelder C et al: Impact of Bevacizumab on parenchymal damage and functional recovery of the liver in patients with colorectal liver metastases. BMC Cancer, 2016; 16: 84

18. Huang G, Lai EC, Lau WY et al: Posthepatectomy HBV reactivation in hepatitis B-related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. Ann Surg, 2013; 257(3): 490–505

19. Oussoultzoglou E, Jaeck D, Addeo P et al: Prediction of mortality rate after major hepatectomy in patients without cirrhosis. Arch Surg, 2010; 145(11): 1075–81

20. Kuramitsu K, Fukumoto T, Kobayashi T et al: The Incidence of posthepatectomy liver failure defined by the International Study Group of liver surgery among living donors. J Gastrointest Surg, 2016; 20(4): 757–64

21. Olthof PB, Coelen RJS, Bennink RJ et al: 99mTc-mebrofenin hepatobiliary scintigraphy predicts liver failure following major liver resection for perihilar cholangiocarcinoma. HPB (Oxford), 2017; 19(10): 850–58