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

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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 Failure

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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\textsubscript{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\textsubscript{R15} test was introduced and popularized by Makuuchi et al. in the 1980s, especially in patients with hepatocellular cancer (HCC) [1]. The ICG\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{R15LIMON}) and ICG plasma disappearance rate (PDR) were noted. The LIMON measurements were converted to conventional spectrophotometric ICG retention rates (ICG\textsubscript{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 cohort 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/m² (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 m² (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 cm³ (range, 929 to 1968) and the preoperative median PLT count was 233000/mm³ (range, 70 100 to 494 000). No significant difference was found between groups regarding preoperative TLV and PLT count[Table 4].

Mean 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 ICG_{R15LIMON} 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_{R15SPECTRO} 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_{R15SPECTRO} 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 ICG_{R15SPECTRO} 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).
|                         | non-PHLF          | PHLF             | p     |
|-------------------------|-------------------|------------------|-------|
| Age                     | 45 (19–72)        | 57 (49–76)       | 0.053 |
| Sex (Male: Female)      | 25: 24            | 2: 2             | n.s.  |
| BMI %                   | 24 (17–33)        | 26 (20–27)       | 0.919 |
| BSA m²                  | 1.79 (1.36–2.18)  | 1.69 (1.58–1.98) | 0.400 |
| TLV ml                  | 1474 (929–1968)   | 1347 (1207–1714) | 0.400 |
| ICG_R15LIMON %          | 1.9 (0.1–13.4)    | 4.1 (1.2–18.4)   | 0.157 |
| PDR %/min               | 26.5 (13.4–48.9)  | 21.4 (11.3–29.5) | 0.178 |
| ICG_R15SPECTRO %        | 5.16 (3.53–16.68) | 21.4 (11.3–29.5) | 0.138 |
| Preop LDH IU/l          | 290 (72–1186)     | 282 (179–798)    | 0.893 |
| Preop CREA mg/dl        | 0.8 (0.5–1.10)    | 0.8 (0.5–1.00)   | 0.865 |
| Preop TBIL mg/dl        | 0.45 (0.21–2.07)  | 0.65 (0.52–0.73) | 0.157 |
| Preop DBIL mg/dl        | 0.16 (0.06–1.88)  | 0.34 (0.26–0.36) | 0.015 |
| ALP IU/l                | 76 (39–358)       | 203 (92–533)     | 0.018 |
| AST IU/l                | 20 (10–220)       | 33 (26–42)       | 0.049 |
| ALT IU/l                | 18 (6–83)         | 32 (24–35)       | 0.125 |
| GGT U/l                 | 17 (70–778)       | 186 (92–315)     | 0.004 |
| INR                     | 1.03 (0.89–1.33)  | 1.11 (0.96–1.28) | 0.244 |
| CRP mg/dl               | 2.18 (0.03–36)    | 18.04 (3.06–42.76)| 0.014 |
| PLT x10⁹/mm³            | 233 (106–494)     | 220 (70.1–310)   | 0.511 |
| Disease                 | Benign: Malign    | 23: 26           | 0.490 |
| Comorbidity (+/-)       | 13/36             | 1/3              | 0.896 |
| Viral serology (+/-)    | 5/44              | 0/4              | 0.502 |
| Status                  | Exitus: Alive    | 1: 48            | 0.147 |
| Pringle time minutes    | 30 (0–65)         | 32 (22–45)       | 1.000 |
| Remnant liver rate %    | 46 (21–99)        | 55 (42–86)       | 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 disappareance 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 | A | B |
| Age years  | 51 | 76 | 49 | 62 |
| Sex        | Male | Male | Female | Female |
| Weight kg  | 80 | 60 | 66 | 62 |
| BMI kg/m²  | 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 & Reconstruct. | Right Hx + VCI repair |
| Hb decrease g/dl | 0.6 | 3 | 1.3 | 45 |
| Pringle’s M min | 45 | 22 | 30 | 18 |
| RLV ml      | 816 | 1118 | 626 | 1151 |
| sFLR %      | 48 | 81 | 50 | 86 |
| RLV %       | 43 | 42 | 48 | 95 |
| ICG₁₅LIMON %| 4.7 | 18.4 | 3.4 | 1.2 |
| ICG₁₅SPECTRO | 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; Recon – reconstruction; Hb – hemoglobin; M – maneuver; min – minutes; RLV – remnant liver volume; sFLR – standardized future liver remnant; ICG₁₅LIMON – Indocyanine green clearance measured by pulse spectrophotometer; ICG₁₅SPECTRO – Indocyanine green clearance value converted to conventional spectrophotometer readings; PDR – Indocyanine plasma disappearance 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\textsubscript{R\textsubscript{15LIMON}}, PDR, and ICG\textsubscript{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\textsubscript{R\textsubscript{15LIMON}} were significantly lower in the LD group (p=0.000, p=0.004, and p=0.034, respectively). In the LD group, median ICG\textsubscript{R\textsubscript{15LIMON}} was 1.6% (range, 0.1 to 5.5), and in the OH group ICG\textsubscript{R\textsubscript{15LIMON}} was 3.4% (range, 0.1 to 18.4). No significant difference was found between groups regarding PDR and ICG\textsubscript{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 hepatocarcinized 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 ICG\textsubscript{R\textsubscript{15LIMON}} PDR, and ICG\textsubscript{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\textsubscript{R\textsubscript{15LIMON}} 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\textsubscript{R\textsubscript{15LIMON}} <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 hepatocellularoma 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 hepatotomy 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.

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Conflicts of interest

None.
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