Interstage Assessment of Remnant Liver Function in ALPPS Using Hepatobiliary Scintigraphy

Prediction of Posthepatectomy Liver Failure and Introduction of the HIBA Index

Matteo Serenari, MD,*† Carlos Collaud, MD,‡ Fernando A. Alvarez, MD,‡
Martin de Santibañes, MD,‡ Diego Giunta, MD,§ Juan Pekolj, MD, PhD, FACS,‡
Victoria Ardiles, MD,‡ and Eduardo de Santibañes, MD, PhD, FACS(Hon), ASA(Hon), ESA(Hon)†

Objective: The aim of this study was to evaluate interstage liver function in associating liver partition and portal vein occlusion for staged hepatectomy (ALPPS) using hepatobiliary scintigraphy (HBS) and whether this may help to predict posthepatectomy liver failure (PHLF).

Background: ALPPS remains controversial given the high rate of liver-related mortality after stage 2. HBS combined with single photon emission computed tomography (SPECT) accurately estimates future liver remnant function and may be useful to predict PHLF.

Methods: Between 2011 and 2016, 20 of 39 patients (51.3%) underwent SPECT-HBS before ALPPS stage 2 for primary (n = 3) or secondary liver tumors (n = 17) at the Hospital Italiano de Buenos Aires (HIBA). PHLF was defined by the International Study Group of Liver Surgery criteria, 50–50 criteria, or peak bilirubin >7 mg/dL. Grade A PHLF was excluded, as it requires no change in clinical management. Receiver-operating characteristic curves were used to determine cutoff for HBS parameters.

Results: Intergastally, 3 HBS parameters differed significantly between patients with (n = 4) and without PHLF (n = 16) after stage 2. Among these, the HIBA-index best predicted PHLF, with a cutoff value of 15%. The risk of PHLF in patients with cutoff <15% was 80%, whereas no patient with cutoff ≥15% developed PHLF.

Conclusions: Interstage HBS could help to predict clinically significant PHLF after ALPPS stage 2. An HIBA-index cutoff of 15% seemed to give the best diagnostic performance. Although further studies are needed to confirm our findings, the routine application of this noninvasive low-cost examination could facilitate decision-making in institutions performing ALPPS.

Keywords: ALPPS, liver failure, scintigraphy

T
he most recent innovation in the field of staged hepatectomies is the associating liver partition and portal vein occlusion for staged hepatectomy (ALPPS) approach,¹ which offers a rapid and large future liver remnant (FLR) hypertrophy that has shown to allow complete tumor removal in a shorter time and in a larger number of patients than classical approaches.² Although we have to wait for long-term outcomes to reveal whether higher resectability rates translate into a survival benefit, the current most important concern with ALPPS is the high mortality rates in most centers.³⁴ Recent results from the ALPPS International Registry showed that 93% of deaths occur after stage 2 and posthepatectomy liver failure (PHLF) remains the most important cause of death.⁴ Although volumetry is the standard method for determining whether a patient can safely undergo a major hepatectomy,⁵,⁶ the ALPPS Registry’s data suggest that FLR sufficiency defined only by classical volumetric criteria is not enough in this scenario, therefore raising the need to investigate more sophisticated tools aiming to evaluate FLR functional reserve. Hepatobiliary scintigraphy (HBS) using dynamic planar acquisitions has been used to estimate FLR function⁷ and to predict both PHLF and liver-related mortality before major hepatectomy.⁸ More recently, single photon emission computed tomography (SPECT) has allowed a more accurate measurement of regional distribution of liver function.⁹

In 2012, we introduced the use of HBS to evaluate liver function during ALPPS as part of a concerted effort to improve safety.¹⁰ Preliminary results from more recent small series suggest that FLR volumetric increase precedes its functional improvement.¹¹–¹³ Although there is agreement that stage 2 should be postponed until a satisfactory function has been reached, the key question yet unanswered is how good the FLR function has to be to avoid PHLF. The aim of the present study was to evaluate interstage liver function in ALPPS using SPECT-HBS with special emphasis in elucidating whether FLR function may predict clinically significant PHLF after completion of ALPPS stage 2.

METHODS

Study Design and Population
The current report represents a single-institution retrospective cohort analysis of a prospectively maintained database. Data for patients submitted to ALPPS at the Hospital Italiano de Buenos Aires (HIBA) between June 2011 and March 2016 were extracted. The ALPPS was indicated and performed as previously described.¹⁴,¹⁵

The study protocol has been registered on ClinicalTrials.gov (identifier NCT02846441). Informed consent was obtained for all patients before surgery and the institutional review board gave ethical approval to perform this study (N2990).

Variables Analyzed

The primary outcome measure was PHLF after ALPPS stage 2, defined as the fulfillment of at least one of the following: International Study Group of Liver Surgery (ISGLS) criteria,¹⁶ 50–50 criteria,¹⁷ or peak bilirubin >7 mg/dL.¹⁸ Clinical severity of PHLF was classified as proposed by the ISGLS.¹⁶ Grade A requires no change of the patient’s clinical management and therefore was not considered in this study.
Data on patient demographics, tumor type, pre/postoperative liver volumetry, liver function, and procedure details were extracted. A compromised liver was defined as presence of at least one of the following: steatosis ≥30%,13 steatohepatitis with a Kleiner-Brunt activity score 2–4,14 sinusoidal dilation grade 2–3 by Rubbia-Brandt score,15 or severe fibrosis/cirrhosis.16 Complications were classified according to Clavien-Dindo22 and major morbidity was defined as grade ≥3a. Any death occurring within 90 days of the postoperative period in the presence of at least 1 PHLF criteria was considered liver-related.

Liver Volumetry
Liver volumes were assessed using computed tomography (CT) or magnetic resonance imaging (MRI) as previously described.8 Volumetric reconstructions were performed both preoperatively and 6 days after stage 1. In case of insufficient hypertrophy, an additional volumetry was performed weekly until a sufficient FLR volume was achieved. Both the FLR and the measured total liver volume (mTLV) were calculated after subtracting the tumor volume. The standardized FLR was defined as the ratio (%) of the FLR volume and the standardized TLV (sTLV) according to the Vauthey formula.24

Hepatobiliary Scintigraphy and HIBA Index
HBS using 99mTc-mebrofenin was generally performed on the same day of CT acquisition, and repeated weekly if stage 2 was delayed. All nuclear medicine equipment and protocols used were the same throughout the study period. Briefly, patients were in supine position, with a large field-of-view (FOV) SPECT-camera (Brightview; Philips) over the liver and heart region. The SPECT-camera was equipped with low-energy high-resolution collimators. First, a dual-head (anterior-posterior) dynamic acquisition (36 frames of 10 s/frame, 128 matrix), which was used for the calculation of the hepatic uptake of mebrofenin, was obtained immediately after the intravenous administration of 259 MBq (7 mCi) 99mTc-labeled (3-bromo-2,4,6-trimethyl-acetanilide) iminodiacetic acid (99mTc-mebrofenin, Bilio-Tec, Tecnonuclear). Note that the radiopharmaceutical was always prepared on-site the same day before injection. Regions of interest (ROIs) were manually drawn by the same experienced operator (C.C.) around the total liver, the heart/large vessels (serving as blood pool), and the total FOV (indicative of total body activity).25 These 3 ROIs were saved to make sure that identical ROIs were used for the anterior and posterior projections (Fig. 1A, B). From these ROIs, 3 different time–activity curves were generated and geometric mean (Gmean) datasets26 for every ROI was calculated using a ROI-ROI calculation: \( \bar{c} = \frac{c_{\text{anterior}} \times c_{\text{posterior}}}{100} \). Measured values were obtained between 150 and 350 seconds post-injection, during a phase of homogenous distribution of the agent in the blood pool before the phase of hepatic excretion.27 Subsequently, a fast SPECT acquisition was performed (60 projections of 4 seconds/projection, 128 matrix), centered on the peak of the hepatic time-activity curve, which was used to calculate the 3-dimensional distribution of function within the liver volume. Separate, volumes of interest (VOIs) around the FLR and the deportedalized liver were manually outlined, using a contrast-enhanced CT-scan linked to the SPECT images as a reference. Extrahepatic bile duct was not included in the liver VOIs.

Three interstage functional parameters were calculated to evaluate their individual capability of predicting PHLF after ALPPS stage 2:

1. Percentage of counts within the FLR (FLR-C): static measure representing the proportion of overall liver function that is produced by the FLR using the 3-dimensional information provided by the SPECT analysis after 350 seconds of radionuclide injection. The FLR-C was calculated dividing the counts (radioactivity) within the FLR’s VOI by the total counts within the entire liver’s VOI (Fig. 1C) using the following formula, expressed as %: FLR-C = \( \frac{\text{FLR counts}}{\text{Total liver counts}} \times 100 \).16

2. The FLR function (FLR-F): dynamic measure representing the proportion of radionuclide cleared from the bloodstream by the FLR per each minute between 150 and 350 seconds post-injection and per square meter of body surface area (BSA).25 The FLR-F was calculated multiplying the total liver function (TL-F) using Gmean datasets, by the FLR-C, and expressed as %/min/m².26

3. The HIBA index (HIBA-i): newly developed dynamic measure representing the proportion of radionuclide accumulated in the FLR during the phase between 150 and 350 seconds post-injection and calculated multiplying the total liver uptake (TL-U) using Gmean datasets by the FLR-C. The TL-U was calculated using the area under the time-activity curve (AUC) of the total liver, without interference from the vascular phase (blood pool) and corrected to the FOV using the following formula, expressed as %: TL-U = \( \frac{\text{AUC total liver}}{\text{AUC FOV}} \times 100 \).

Statistical Analysis
Data are expressed as median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. The Mann–Whitney U test was used for comparison of continuous variables and Chi-squared test or Fisher exact test was used for comparisons of categorical variables between patients with and without PHLF. Correlation between variables was tested using the Pearson correlation coefficient \( r \). Receiver-operating curve (ROC) analysis was used to identify a cutoff value for prediction PHLF for the 3 functional parameters. Sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios were calculated. A logistic regression model to predict the expected values of PHLF was built using HIBA-i as independent variable. All statistical tests were 2-tailed, and differences were considered significant at a \( P \leq 0.05 \). Statistical analysis was performed with SPSS Version 13.0 (SPSS Inc, Chicago, IL).

RESULTS
Patient Characteristics and Outcomes
A total of 39 patients underwent the ALPPS approach during the study period, of whom 20 (51.3%) were submitted to both CT-volumetry and SPECT-HBS before completion of stage 2, therefore representing the final study population. Overall, there were 12 males and the median age was 61 years (IQR = 46–71). Sixteen patients (80%) had colorectal metastases, 1 breast cancer metastasis, 1 hepatocellular carcinoma, 1 gallbladder cancer, and 1 perihilar cholangiocarcinoma. Fifteen patients (75%) received a median of 5 cycles (IQR = 1–7) of preoperative chemotherapy. Right trisectioectomy was performed in 14 patients (70%) and right hepatectomy in 6 (30%).

Major morbidity after stage 1 was 25%. One patient developed interstage PHLF, according to peak bilirubin >7 criteria. After stage 2, major morbidity was 25% and 4 patients developed PHLF: 1 patient according to only peak bilirubin criteria and 3 patients according to ISGLS, 50–50, and peak bilirubin criteria (grade B and 1 grade C). One death occurred 20 days after stage 2 because of irreversible PHLF in a 67-year-old male with a gallbladder cancer. All patients who developed PHLF were distributed homogeneously during the study period. Demographic and intraoperative characteristics of patients with (n = 4) and without PHLF (n = 16) after stage 2 are summarized in Table 1.19–22 All patients with PHLF were
transfused during stage 2 and submitted to right trisectionectomy compared to 50% and 62.5%, respectively, in the group without PHLF. Even though patients without PHLF had a nonsignificant lower rate of trisectionectomies, FLR clean-up was performed in 13 patients (81%), and more specifically in 5 of 6 patients who underwent a right hepatectomy. This included a left lateral sectionectomy leaving only S4 as FLR in 1 patient.

**Volumetric Analysis**

Preoperatively, median FLR/STLV and FLR/body weight were 24% (IQR = 19–27) and 0.53% (IQR = 0.40–0.58), respectively. Last CT-volumetry before completion of hepatectomy was performed in median 11 days (IQR = 6–20) from stage 1. Median FLR/STLV and FLR/body weight before stage 2 were 40% (IQR = 35–48) and 0.87% (IQR = 0.78–1.05) respectively, without significant differences when comparing patients with and without PHLF (Table 2).

**Functional Analysis**

HBS was performed in median 3 days before stage 2 (IQR = 1–5). Median TL-F and TL-U was 5.04%/min/m² (IQR = 3.66–5.77) and 55% (IQR = 45–62), respectively. Median FLR-C was 39% (IQR = 31–48) and showed a good correlation (r = 0.772; P < 0.0001) with its volumetric counterpart FLR/mTLV, whose median value was 39% (IQR = 35–46). Range between these 2 parameters was wide and included both positive and negative differences (−10% to +14%), with volume overestimating function in 12 of 20 patients.

When comparing patients with and without PHLF after stage 2 (Table 2), FLR-C was significantly lower in the PHLF group (P = 0.011) as well as FLR-F and HIBA-i (P = 0.011 and P = 0.001, respectively). The only patient who died had the lowest value of both FLR-F and HIBA-i.

**Safe Cutoff for Liver Function and Probability of PHLF**

ROC analysis revealed that a cutoff value for HIBA-i of 14.94% was able to better identify (AUC = 0.98) patients who developed PHLF than the other parameters (Fig. 2). The predicting risk of PHLF in patients with a HIBA-i <15% was 80%, whereas no patient with a HIBA-i >15% developed PHLF (Fig. 3). Table 3 summarizes the diagnostic accuracy of the 3 different functional parameters.

**DISCUSSION**

The present study on the largest series of HBS in ALPPS published to date is the first to explore the value of SPECT-HBS in predicting the risk of PHLF. To this aim, we developed a new formula to measure FLR sectorial function, the HIBA-i. The findings obtained indicated that an interstage HIBA-i of ≤15% was the most accurate scintigraphic parameter to predict clinically significant PHLF after ALPPS stage 2.

During the first ALPPS Consensus Meeting held in Hamburg in February 2015, it was stated that stage 2 should be completed following the already accepted volumetric standards used for major hepatectomies. Nevertheless, the reported incidence of PHLF in the International Registry ranged from 16% to 31% even when theoretically sufficient FLR volumes were achieved. Furthermore, 75% of 90-day mortalities were liver-related and a decrease of liver function between stages, reflected by peak of bilirubin >5 mg/dL or a MELD score >10, was found to be an independent predictor of poor outcome regardless of FLR size. But, why do we find ourselves back at square one, struggling against the same foe we were supposed to control with this new proposal? One possible explanation for this dilemma could be the fact that rapid volumetric increase during ALPPS may not be immediately corresponded by an equal functional increase, as recently suggested by histologic hepatocyte immaturity in FLR parenchyma and volume overestimating function in 60% of patients in the present series.

Regarding the use of HBS in ALPPS, besides our experience, only small case series have been published. A Japanese group reported that FLR functional increase with ALPPS, assessed by Tc-GSA SPECT-scintigraphy, tended to be less than with classical 2-stage hepatectomy despite a sufficient FLR volumetric increase. However, Tc-GSA is not available in western countries, where Tc-mebrofenin is preferred to estimate liver function because of its higher liver uptake, very low renal excretion, and high resistance to displacement by high bilirubin levels. Regarding Tc-mebrofenin HBS in ALPPS, a recent letter by Truant et al including data from 5 patients indicated a diffuse drop of liver function after stage 1 in patients suffering from PHLF and a functional loss in the excluded liver sharper than the FLR.
functional gain in the only deceased patient. Even though we did not measure TL-F before stage 1, the interstage median value of 5.04%/min/m² was lower than reported in other series, which prompts us to believe that a slight decrease may occur after stage 1 probably because of the deportalized liver left in place or the release of several inflammatory cytokines. Another explication might be related to different ways of manufacturing radionuclides or process for radiopharmaceutical preparations, thus resulting in lower values than those reported from other groups. Despite the existence of the Japanese and French experiences above-mentioned, clinically relevant data regarding the capability of HBS in predicting PHLF have not yet been provided. We have previously described how FLR-C might help to define when and whether to proceed to ALPPS stage 2. However, FLR-C does not contain the information regarding how that liver really works. As an example, even though the only patient who died in the present series had a 34.5% FLR-C, his TL-F was far lower (1.28%/min/m²) than the median value of the entire cohort (5.04%/min/m²), thus resulting in a very

### TABLE 1. Characteristics of Patients With and Without PHLF

<table>
<thead>
<tr>
<th>Variable</th>
<th>PHLF, Yes (n = 4)</th>
<th>PHLF, No (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>61 (50–74)</td>
<td>61 (44–71)</td>
<td>0.820</td>
</tr>
<tr>
<td>Sex, female/male, n</td>
<td>1/3</td>
<td>7/9</td>
<td>0.619</td>
</tr>
<tr>
<td>Charlson Index (1–14), median (IQR), n</td>
<td>6 (5–8)</td>
<td>8 (6–9)</td>
<td>0.148</td>
</tr>
<tr>
<td>BMI, median (IQR), kg/m²</td>
<td>25 (21.1–30.1)</td>
<td>23.9 (21.7–26)</td>
<td>0.682</td>
</tr>
<tr>
<td>Preoperative chemotherapy, n (%)</td>
<td>2 (50)</td>
<td>13 (65)</td>
<td>0.249</td>
</tr>
<tr>
<td>Cycles of chemotherapy, median (IQR), n</td>
<td>9 (2–12)</td>
<td>5 (2–7)</td>
<td>0.494</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>METS</td>
<td>2 (50)</td>
<td>14 (87.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>Biliary</td>
<td>2 (50)</td>
<td>3 (18.7)</td>
<td>0.249</td>
</tr>
<tr>
<td>Diseased Parenchyma, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis &gt; 30%</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Steatohepatitis ≥ grade 4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SOS ≥ grade 2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fibrosis ≥ grade 5</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Intraoperative data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of liver resection, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hepatectomy</td>
<td>0</td>
<td>6 (37.5)</td>
<td>0.267</td>
</tr>
<tr>
<td>Right trisectionectomy</td>
<td>4 (100)</td>
<td>10 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Partial parenchymal transection, n (%)</td>
<td>2 (50)</td>
<td>13 (81.3)</td>
<td>0.249</td>
</tr>
<tr>
<td>Mini-ALPPS approach, n (%)</td>
<td>0</td>
<td>5 (31.3)</td>
<td>0.530</td>
</tr>
<tr>
<td>Associated procedure, n (%)</td>
<td>3 (75)</td>
<td>7 (43.8)</td>
<td>0.582</td>
</tr>
<tr>
<td>Patients transfused, n (%)</td>
<td>4 (100)</td>
<td>8 (50)</td>
<td>0.117</td>
</tr>
<tr>
<td>Pringle maneuver, n (%)</td>
<td>1 (25)</td>
<td>3 (18.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHLF interstage, n (%)</td>
<td>1 (25)</td>
<td>0</td>
<td>0.200</td>
</tr>
<tr>
<td>Morbidity ≥ 3a stage 1, n (%)</td>
<td>1 (25)</td>
<td>4 (25)</td>
<td>1.000</td>
</tr>
<tr>
<td>Morbidity ≥ 3a stage 2, n (%)</td>
<td>2 (50)</td>
<td>3 (18.8)</td>
<td>0.249</td>
</tr>
<tr>
<td>90-day mortality, n (%)</td>
<td>1 (25)</td>
<td>0</td>
<td>0.400</td>
</tr>
<tr>
<td>Hospital stay, median (IQR), days</td>
<td>23 (14–31)</td>
<td>20 (14–35)</td>
<td>0.963</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HCC, hepatocellular carcinoma; METS, metastases; SOS, sinusoidal obstruction syndrome.

According to the Kleiner–Brunt NASH activity score.\(^1\)

According to Rubbia–Brandt et al.\(^2\)

According to the Ishak Score.\(^3\)

According to Clavien-Dindo et al.\(^4\)

### TABLE 2. Volumetric and Functional Assessment Before Stage 2 in Patients With and Without PHLF

<table>
<thead>
<tr>
<th>Variable</th>
<th>PHLF, Yes (n = 4)</th>
<th>PHLF, No (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver volumes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLR/sTLV, median (IQR), %</td>
<td>35 (28–42)</td>
<td>42 (38–50)</td>
<td>0.148</td>
</tr>
<tr>
<td>FLR/mTLV, median (IQR), %</td>
<td>34 (32–42)</td>
<td>41 (36–47)</td>
<td>0.148</td>
</tr>
<tr>
<td>FLR/BW, median (IQR), %</td>
<td>0.74 (0.57–0.89)</td>
<td>0.88 (0.8–1.08)</td>
<td>0.178</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLR-C, median (IQR), %</td>
<td>30 (25–34)</td>
<td>41 (35–52)</td>
<td>0.011</td>
</tr>
<tr>
<td>FLR-F, median (IQR), %/min/m²</td>
<td>0.94 (0.55–1.50)</td>
<td>2.07 (1.56–2.37)</td>
<td>0.011</td>
</tr>
<tr>
<td>HIBA-i, median (IQR), %</td>
<td>12.86 (12.28–14.18)</td>
<td>23.29 (20.34–27.12)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BW indicates body weight.
The HIBA-i could be considered a simplification of the Ekman's algorithm,
35 calculated in a similar way to that reported in the past for auxiliary liver transplantation.38,39 In ALPPS, however, dynamic analysis cannot take into account separately the uptake within the excluded segments and the FLR because of a superimposition in the planar view of the 2 hemilivers; therefore, 1 single ROI was drawn around the entire liver area to measure TL-U. The estimated proportion of TL-U represented by the FLR (HIBA-i) was defined by the 3-dimensional information provided by SPECT's VOIs analysis. There are 2 main differences of HIBA-i compared with FLR-F as originally proposed by the AMC group.8 First, we have used Gmean datasets and SPECT instead of only anterior view projections, FLR-F is significantly overestimated if FLR is represented by left liver segments.26 Such an overestimation results increased in ALPPS since right posterior segments are displaced more dorsally than normal livers secondary to full liver mobilization and enlarged left FLR hypertrophy. Thereby, the right lobe may be in some cases practically not represented in the anterior view, leading to a more pronounced overestimation of the FLR-C. In our series, right or right extended hepatectomies represented the 100% of our patients, as well as 40 of 55 (72.7%) consecutive hepatectomies reported by De Graaf et al.,8 thus contributing to an important bias. Secondly, even though a 57% positive predictive value represents a safe threshold when using the cutoff of 2.69%/min/m²,8 it also means that about 43% of patients are false-positive, leading to unnecessary preoperative PVE and extra hospitals costs.35 In ALPPS, specificity should be maximized if HBS wants to be used as a confirmatory test. Thirdly, ROIs/VOIs drawing both in the dynamic and SPECT phase, as well as misregistration errors, could lead to potential bias in calculation, even if performed by the same operator.36 Therefore, standardization of the technique and use of a shared imaging software seem in our opinion of utmost importance to enable comparisons among different centers.37 For all these reasons, we proposed a novel index for calculating FLR function in ALPPS, the HIBA-i.

FIGURE 2. ROC curves of 3 interstage liver function parameters, which differed significantly between patients with and without PHLF. (A) HIBA-i; (B) number of counts in the remnant liver by total number of counts (FLR-C). (C) FLR-F. AUC indicates area under the curve; cutoff value giving equal weight to sensitivity and specificity.

low FLR-F (0.44%/min/m²). For this reason, although a FLR-C >35% may be safe, at present we do not recommend to use this single parameter to decide whether or not completing stage 2. Instead, as in the present study, other HBS parameters based on radionuclide parenchymal uptake should be applied.

Measurement of liver uptake function by N 2,6 diethyl-3-iodo-phenyl carbamoyl iminodiacetic acid (IODIDA) clearance rate was first described in 1992 by Ekman et al.25 Two decades later, the Academic Medical Center (AMC) group in Amsterdam established 1 single cutoff for FLR-F of 2.69%/min/m², able to predict PHLF in patients submitted to major hepatectomy regardless of the presence of parenchymal disease.3 The ROC curve analysis in our study established a FLR-F cutoff of 1.69%/min/m². Such cutoff was far lower than provided by De Graaf et al.,8 which could be explained in several ways. First, the values obtained by the AMC group were derived from single-head gamma-camera using only data from anterior projection and without the use of SPECT. Nowadays, data from anterior and posterior projections can be estimated and combined with SPECT analysis.3 When using only data from the anterior projection, FLR-F is significantly overestimated if FLR is represented by left liver segments.26 Such an overestimation increases in ALPPS since right posterior segments are displaced more dorsally than normal livers secondary to full liver mobilization and enlarged left FLR hypertrophy. Thereby, the right lobe may be in some cases practically not represented in the anterior view, leading to a more pronounced overestimation of the FLR-C. In our series, right or right extended hepatectomies represented the 100% of our patients, as well as 40 of 55 (72.7%) consecutive hepatectomies reported by De Graaf et al.,8 thus contributing to an important bias. Secondly, even though a 57% positive predictive value represents a safe threshold when using the cutoff of 2.69%/min/m²,8 it also means that about 43% of patients are false-positive, leading to unnecessary preoperative PVE and extra hospitals costs.35 In ALPPS, specificity should be maximized if HBS wants to be used as a confirmatory test. Thirdly, ROIs/VOIs drawing both in the dynamic and SPECT phase, as well as misregistration errors, could lead to potential bias in calculation, even if performed by the same operator.36 Therefore, standardization of the technique and use of a shared imaging software seem in our opinion of utmost importance to enable comparisons among different centers.37 For all these reasons, we proposed a novel index for calculating FLR function in ALPPS, the HIBA-i.

FIGURE 3. Box plot showing the distribution of each functional parameter between patients with and without PHLF. (A) Median HIBA-i was 12.86% (range = 12.18–14.53) in patients with PHLF vs 23.29% (range = 14.42–37.26) in patients without PHLF. (B) Median FLR-C was 30% (range = 24–35) in patients with PHLF vs 41% (range = 29–59) in patients without PHLF. (C) Median FLR-F was 0.94%/min/m² (range = 0.44–1.67) in patients with PHLF vs 2.07%/min/m² (range = 0.47–3.21) in patients without PHLF.
TABLE 3. Different Functional Parameters and Their Diagnostic Accuracy in Predicting PHLF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff</th>
<th>AUC</th>
<th>95% CI</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLR-F, %/min/m²</td>
<td>1.69</td>
<td>0.91</td>
<td>0.77–1</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>100</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>FLR-C, %</td>
<td>34.5</td>
<td>0.91</td>
<td>0.77–1</td>
<td>100</td>
<td>82</td>
<td>50</td>
<td>100</td>
<td>5.3</td>
<td>0</td>
</tr>
<tr>
<td>HIBA-i, %</td>
<td>14.94</td>
<td>0.98</td>
<td>0.94–1</td>
<td>100</td>
<td>94</td>
<td>80</td>
<td>100</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

LR+ indicates likelihood ratio positive; LR-, likelihood ratio negative; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

CONCLUSION

The present study, focused on the value of interstage SPECT-HIBS in predicting risk of PHLF after ALPPS stage 2, found an HIBA-i of <15% to best predict clinically significant PHLF in patients with an already sufficient FLR volume. However, as it is unlikely to avoid PHLF based on a single criterion (either volumetric or functional), other already known risk factors such as patient’s age, tumor type, occurrence of liver failure, and/or surgical complications between stages should also be taken into account to guide decision-making in ALPPS. Even though further studies are needed to confirm our findings, given the increasing evidence supporting the use of HBS to quantify sectorial liver function, we encourage the routine use of this complementary noninvasive low-cost examination in institutions performing the ALPPS approach as an effort to continue improving the safety of this surgical innovation.

REFERENCES

© 2017 Wolters Kluwer Health, Inc. All rights reserved. www.annalsofsurgery.com | 7

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.