Non-invasive tests for the prediction of post-hepatectomy liver failure in the elderly

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Abstract

Post-hepatectomy liver failure (PHLF) is associated with great morbidity and mortality after resection of hepatocellular carcinoma. Previous studies have underlined that advanced age could be a potential factor influencing post-operative complications and long-term survival.

In the past, candidates for resection were based on the Child-Pugh classification, the predictive value of which was rather low. The selection of patients undergoing resection in Western countries is based on the assessment of portal hypertension (PH), which is clinically assessed by measurement of the hepatic venous pressure gradient, an invasive and costly process. Thus, there have been several attempts to identify the best non-invasive test (NIT) to accurately predict PHLF. Most biochemical NITs for the prediction of PHLF are focused on evaluation of underlying liver cirrhosis and PH. Amongst them, FIB-4, which also includes the patient's age, seems to have more robust supporting results. In Europe and the USA., the most tested and reliable NIT for predicting PHLF is the evaluation of liver stiffness measurement, which is also influenced by age. Imaging parameters are promising tools which are used only in specialized centers however, and when available. Liver volume parameters, as well as contrast-enhanced data, demonstrate good accuracy in predicting PHLF. In this scenario, the evaluation of sarcopenia and bone mineral density through contextual imaging allows the delineation of PHLF in at-risk elderly patients. Further studies focused on parameters for the evaluation of PHLF in elderly patients are needed.

Keywords: Post-hepatectomy liver failure, liver resection, elderly, liver stiffness measurement, indocyanine green retention test
INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common cause of death in patients with cirrhosis\(^1\). Despite numerous therapeutic options, the only curative treatments are liver transplantation and hepatectomy\(^2\). Patients with a single HCC nodule, Child-Pugh class A, normal bilirubin (< 1 mg/dL) and without portal hypertension have the best prognosis and are ideal candidates for liver resection.

The presence of clinically significant portal hypertension (CSPH) (port-hepatic pressure gradient greater than 12 mmHg) or clinical manifestation (platelet count < 100,000/mL, associated with splenomegaly or esophageal varices) appears to be associated with a worse prognosis, but does not preclude resection in selected patients\(^3,4\). Thus, patients with cirrhosis should be carefully selected to reduce the risk of postoperative liver failure and death. Post-hepatectomy liver failure (PHLF) is still a major concern for liver surgeons\(^2\). In the last few years, there has been an increasing need for a simple and accurate tool for evaluating liver function before surgery to minimize PHLF and postoperative mortality\(^5\). It is difficult to define PHLF exactly since it manifests with one or more of these features: ascites, jaundice, coagulopathy or kidney failure. The most commonly used criteria for defining PHLF are the 50-50 Criteria where PHLF is defined as total serum bilirubin > 50 mmol/L 5 days after surgery or thereafter and an international normalized ratio (INR) > 1.7\(^6\). Other diagnostic criteria are the peak bilirubin > 7 mg/dL in any postoperative period, in the absence of cholestasis, and the International Study Group of Liver Surgery (ISGLS) criteria that define PHLF by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5\(^7\).

In the past, the selection of candidates for resection was based on the Child-Pugh classification but its predictive value has been determined to be insufficient. Japanese groups use the indocyanine green retention test (ICG), which has proved to be more reliable than Child-Pugh and the Model for End-stage Liver Disease (MELD) to predict PHLF\(^8,9\). In Western countries, the selection of candidates for resection is usually based on the assessment of portal hypertension, which is clinically assessed by measurement of the hepatic venous pressure gradient (HVPG > 10 mmHg)\(^10\). However, these methods are invasive and costly. Thus, several authors have tried to evaluate other non-invasive methods including biochemical scores, the measurement of liver and spleen stiffness (LSM and SSM) and imaging patterns as predictors of PHLF\(^8,11-14\).

With an increase in life expectancy and improvement in operative safety and efficacy of hepatic resection techniques, surgeons should also evaluate the best surgical option in elderly patients\(^15\). Indeed, previous studies have implicated older age as a potential factor influencing post-resection complications and survival, and are summarized in a recent systematic review and meta-analysis\(^15\) which concluded that age > 70 was associated with increased 30-day and overall mortality when compared with non-elderly cohorts. A promising factor that also influences post-operative outcomes is patient frailty, defined as a syndrome characterized by decreased physiological reserves. Only one study has reported a specific association between frailty and PHLF\(^16\). However, frailty assessment is based on a self-reporting questionnaire, which could be affected by several biases.

Thus, this review aims to summarize the recent advances on objective parameters such as non-invasive tests (NITs) for predicting PHLF, particularly in elderly patients.

BIOCHEMICAL SCORES

Fibrosis and liver functional reserve scores  

\(FIB-4\)

The Fibrosis (FIB)-4 index was first proposed by Sterling and colleagues\(^17\) and is based on four factors included in the following equation: \([\text{age(years) } \times \text{AST(UI/L)}/\text{platelet count } \times \text{ALT(UI/L)}]\). It is a non-
invasive predictor of the progression of fibrosis in patients with chronic viral hepatitis. Over the years, several studies have validated its role as a marker of hepatic fibrosis\textsuperscript{[18,19]}.

An important study\textsuperscript{[20]} indicated that the Fib-4 index not only demonstrated the best predictive ability for cirrhosis, but it was also an independent prognostic factor for postoperative hepatic insufficiency, overall survival, and disease-free survival for HCC patients with radical liver resection. They also stratified patients, with the cut-off value of 3.15, into Low and High fibrosis-4 groups. The High fibrosis-4 group had a higher mean age (56.3 ± 10.4 vs. 47.7 ± 11.7, \(P < 0.01\)), higher MELD score (\(P = 0.001\)), and more patients with Child-Pugh grade B (7.4% vs. 4.0%, \(P = 0.037\)).

These results have also been confirmed by other studies\textsuperscript{[21]}. Other groups have tried to use the ratio of the remaining liver volume (FLRVR) and FIB-4 to predict PHLF and showed that FLRVR/FIB-4 was an independent predictive factor of outcomes after liver resection in cirrhotic patients\textsuperscript{[22]}. The most recent study by Zhou \textit{et al.}\textsuperscript{[23]} demonstrated that the FIB-4 index was a more accurate predictive factor for PHLF and survival than the Child-Pugh score; the authors thus proposed the use of the FIB-4 index to perform pre-hepatectomy assessment citing a low incidence of PHLF in patients with FIB-4 ≤ 4.16. On the other hand, Zhang \textit{et al.}\textsuperscript{[24]} showed that FIB-4 was an independent predictor of PHLF only in minor hepatectomy patients. Multivariate analysis in this subgroup of patients revealed that age (the older the patient, the more the risk), Child-Pugh score and Albumin-Bilirubin score/spleen thickness ratio (ALBI/ST) were predictors of PHLF in the APRI model, while Child-Pugh score, FIB-4, and ALBI/ST were found to be significant risk factors of PHLF in the FIB-4 model. Thus, it is possible to conclude that FIB-4 is able to predict PHLF since it is related not only to the degree of liver fibrosis but also, to the general performance of the patient since it includes age.

\textit{Lok Index and Forns Index}

The Lok Index and Forns Index are two other non-invasive markers of fibrosis. The Lok index is a non-invasive tool introduced by an American research group\textsuperscript{[25]} as a predictor of cirrhosis development in patients with chronic HCV-hepatitis. It is based on simple laboratory parameters and calculated through the following formula: \(\log \text{odds (predicting cirrhosis)} = 5.56 - 0.0089 \times \text{platelet count (} \times 10^3/\text{mm}^3) + 1.26 \times \text{AST/ALT ratio} + 5.27 \times \text{INR}\). Some studies have correlated the value of the Lok index with the grade of fibrosis. For example, Ma \textit{et al.}\textsuperscript{[26]} showed that FIB-4 and Lok’s model were the most effective models for distinguishing significant and extensive fibrosis. Zhou \textit{et al.}\textsuperscript{[27]} found that a Lok index cut-off value of 0.4531 could further spare 24.2% of gastroscopies without missing high-risk varices (HRVs)\textsuperscript{[27]}. Since this is a fibrosis marker, Mobarak \textit{et al.}\textsuperscript{[28]} found that it was also able to predict HCC development. To date, the Lok-index is predominantly used for the prediction of fibrosis and cirrhosis but not PHLF.

The Forns Index was developed by Forns \textit{et al.}\textsuperscript{[29]} in 2002, before the introduction of transient elastography techniques. It was first proposed as a non-invasive tool for the detection of patients with non-significant liver fibrosis. It is calculated using four variables (age, gamma glutamyl transferase, total cholesterol and platelet count) with the following formula: \(7.811 - 3.131 \times \ln \text{[platelet count (} \times 10^9/L]} + 0.781 \times \ln \text{[gamma GT (IU/L)]} + 3.467 \times \ln \text{[age (years)]} - 0.014 \times \text{[cholesterol (mg/dL)]}\). The first studies on the Forns Index (FI) highlighted its accuracy in identifying patients with different stages of fibrosis and cirrhosis\textsuperscript{[29,30]}. A recent study showed that the Forns index is also useful in evaluating liver functionality and the degree of liver fibrosis, so it is able to predict HCC recurrence and patient survival\textsuperscript{[31]}. However, to date, little is known on the use of the Forns index to predict PHLF.

\textit{ALBI score}

Another biochemical index used in clinical practice is the Albumin-Bilirubin (ALBI) score, which was introduced by Johnson \textit{et al.}\textsuperscript{[32]} to evaluate liver function in patients with hepatocellular carcinoma. It was
initially proposed as an alternative to the Child-Pugh score, which has some limitations, such as the inclusion of non-objective parameters (ascites, encephalopathy). However, the ALBI score was also able to predict the severity and long-term prognosis of patients with chronic liver disease\cite{33}. In particular, it was found to be a reliable prognostic tool in assessing short-term outcomes in hepatic decompensation\cite{34}, in predicting in-hospital mortality in patients with acute upper gastrointestinal bleeding\cite{35} and as a prognostic factor in HCC patients\cite{36}. The ALBI score is based on serum levels of albumin and total bilirubin and can be calculated through the following formula: (\log_{10} \text{bilirubin} \, \mu \text{mol/L} \times 0.66) + (\text{albumin} \, \text{g/L} \times -0.0852). It was further categorized into three different grades: grade 3 (> - 1.39), grade 2 (> - 2.60 to ≤ - 1.39), and grade 1 (≤ - 2.60).\cite{32}

The ALBI grade was also a significant prognostic factor for PHLF in HCC patients\cite{5}. In a comparative study\cite{37}, the ALBI score showed superior predictive value of PHLF over the Child-Pugh score, MELD score and ICG R15. The area under the ROC curve (AUC) of the ALBI score (AUC 0.745) for predicting PHLF was significantly higher than that of the Child-Pugh score (AUC 0.665), MELD score (AUC 0.649) and ICG R15 (AUC 0.668). With a cut-off value of the ALBI score of -2.303, it was possible to reach a sensitivity of 77.3% and a specificity of 64.0% for predicting PHLF\cite{37}. Another group\cite{24} associated the ALBI score with spleen thickness (ST) as a surrogate of portal hypertension. In this study, they compared the predictive ability of ALBI/ST with FIB-4 and APRI and found that ALBI/ST had a higher diagnostic accuracy for PHLF than FIB-4 and APRI. The AUC for the ALBI/ST ratio (AUC = 0.774, P < 0.001) was larger than that of FIB-4 (AUC = 0.696, P < 0.001), APRI (AUC = 0.697, P < 0.001), ALBI (AUC = 0.701, P < 0.001), and ST (AUC = 0.710, P < 0.001)\cite{24}. Also, in this study, multivariate analysis in the minor hepatectomy subgroup revealed that age, Child-Pugh score and ALBI/ST and Child-Pugh score, FIB-4, and ALBI/ST were significant predictors of PHLF in the APRI and FIB-4 models respectively. However, a study conducted by Zhang et al.\cite{5} showed that the ALBI grade was a good predictor of overall survival in BCLC stage 0/A patients but not in other BCLC stages. Thus, it is possible to conclude that the novel ALBI score is certainly one of the most validated scores for predicting PHLF, as described in Table 1\cite{5,33,45,37-44}.

**Table 1. Studies evaluating ALBI score in predicting PHLF**

| Authors          | Country     | Population | Etiology | Outcome                  | Nr. cases | ALBI cut-off | AUROC |
|------------------|-------------|------------|----------|--------------------------|-----------|--------------|-------|
| Toyoda et al.\cite{38}, 2016 | Asia/Europe | 1,148      | Mixed    | Death                    | N/A       | -2.60        | N/A   |
| Wang et al.\cite{39}, 2016 | China       | 1,242      | 85% HBV  | PHLF                     | 166       | -2.77        | 0.723 |
| Ke et al.\cite{40}, 2016    | China       | 372        | 80% HBV  | Postoperative complications | 166     | N/A          | 0.721 |
| Andreasot et al.\cite{41}, 2017 | USA       | 2,659      | N/A      | PHLF                     | 149       | -2.60/-1.39  | N/A   |
| Li et al.\cite{42}, 2017    | China       | 491        | 83% HBV  | Postoperative complications | 270     | -2.45        | 0.647 |
| Russolillo et al.\cite{43}, 2019 | Italy     | 400        | 40% HCV  | Overall morbidity, PHLF  | 176       | -2.60/-1.39  | N/A   |
| Bölin et al.\cite{44}, 2018 | Croatia     | 38         | 84% ALD  | Death                    | 24        | N/A          | N/A   |
| Zhang et al.\cite{45}, 2018 | China       | 338        | 82% HBV  | PHLF                     | 26        | -2.44        | 0.782 |
| Zou et al.\cite{46}, 2018   | China       | 473        | 85% HBV  | PHLF                     | 50        | -2.303       | 0.745 |
| Mai et al.\cite{47}, 2019   | China       | 1,055      | HBV      | PHLF                     | 151       | -2.77        | 0.717 |

ALBI: Albumin-bilirubin; ALD: alcoholic liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; N/A: not available; PHLF: post-hepatectomy liver failure

**Indocyanine Green Retention Test**

The clearance of indocyanine green (ICG) is a test used to assess liver excretory function quantitatively. ICG is a water-soluble fluorescent dye, which totally binds to albumin and β-lipoprotein in the blood and is exclusively taken up by hepatocytes and excreted unmodified in bile, without entero-hepatic circulation\cite{46,47}. Thus, its clearance depends on several factors: hepatic blood flow, the function of the hepatocytes and biliary excretion\cite{46,47}. However, this test takes time and is uncomfortable for patients. Thus, a faster sampling method was subsequently introduced, the ICG 15-min retention test (ICG-r15), consisting of an injection of an ICG bolus and peripheral venous blood sampling every 5 min for 20 min\cite{48,49}. In the last few decades, a noninvasive ICG measurement by spectrophotometry, called LiMON® (Pulsion Medical System, Munich,
Germany), was developed. The device uses a finger optical probe, which detects, after ICG infusion, the fractional pulsatile changes in optical absorption. The device has already been validated in several studies [50,51] with good correlation with ICG-r15 results, comparable with correction of a mathematical formula [50].

Since ICG clearance depends on blood flow, it was associated with portal hypertension [48] and liver function for its pharmacokinetics (uptake and excretion through the hepatocytes) as well [47,52-54]. Thus, in Eastern countries it is considered an accurate method to assess liver functional reserve pre-operatively and has been used for almost 30 years [47] ; on the other hand, in Western countries, it is not widely used because it is highly influenced by hepatic blood flow [47] and thus, by other conditions that could affect it.

The normal ICG-r15 value is about 10% [55]. The ICG-r15 reported cut-off for performing a safe major hepatectomy is between 14% and 17%, the latter in younger patients with milder liver disease [56,57]. Other authors have reported different cut-offs of 14% and 23% for safe major and minor hepatectomy respectively [55,58]. In another previous study [57] with age and sex-matched patients, the authors found no difference in terms of PHLF and mortality between patients with ICG-r15 of more than, and less than 14% who have undergone major hepatectomy. However, to date, the reported upper limit of ICG-r15 for considering liver resection is 40% [58]. The accuracy of ICG-r15 in predicting PHLF could be increased with the combination of bilirubin levels and ascites [56]. Several authors comparing the performance of ICG-r15 with other parameters found that it was superior to MELD [60] and that the combination with platelet count, portal hypertension (ICG-r15 cut-off value of 7.1%, sensitivity 52.2% and specificity 89.5%) [44] and Child-Pugh stage [61] was able to improve its accuracy. Moreover, liver stiffness measurement (LSM) was also found to correlate with ICG-r15 and to provide additional information on the prognosis of the patient [62]. Other authors have found good correlation when comparing ICG-r15 with the degree of portal hypertension [48,54].

In conclusion, no definitive lower ICG-r15 cut-offs for distinguishing between safe minor or major hepatectomy are currently available, as shown in Table 2 [6,37,57,64-67]; major hepatectomy in the presence of unsatisfactory ICG-r15 results should be performed only in high-volume centers. ICG-r15 could be considered a good marker of liver function and indirectly, of the degree of portal hypertension. Further studies are needed however, for this latter association.

### Portal hypertension scores

**Plated to spleen stiffness ratio PSR**

Another widely used biochemical score is the PSR (platelet count-to-spleen ratio), which consists of the ratio between PLT (expressed in number/mm$^3$) and spleen diameter (mm) [69]. The PSR value is strictly

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| Authors      | Country         | Population | Etiology | Outcome                  | Nr. cases | Technique      | ICG cut-off | AUROC |
|--------------|-----------------|------------|----------|--------------------------|-----------|----------------|-------------|-------|
| Kitano et al. [63], 1997 | Japan          | 54         | N/A      | Hospital mortality       | 7         | ICG-r15        | 14%         | N/A   |
| Lau et al. [54], 1997 | Hong Kong      | 127        | N/A      | Death                    | 14        | ICG-r15        | 14% (major hep.) | N/A  |
| Lam et al. [57], 1999 | Hong Kong      | 117        | N/A      | Postoperative complications | N/A | ICG-r15        | 14%         | N/A   |
| Hsia et al. [54], 2000 | Taiwan         | 168        | Mixed    | Morbidity                | 51        | ICG-r15        | <10%/ >20%  | N/A   |
| Lao et al. [56], 2005 | China          | 255        | N/A      | Death                    | N/A       | ICG-r15        | 10-20%      | N/A   |
| Zhou et al. [57], 2018 | China          | 473        | 85% HBV  | PHLF                     | 50        | ICG-r15        | N/A         | 0.668 |
| Hwang et al. [58], 2015 | South Korea    | 723        | 81% HBV  | Death from PHLF          | 6         | FRL-kICG       | <0.05       | N/A   |
| Wang et al. [59], 2018 | China          | 185        | 83% HBV  | Severe PHLF              | 23        | ICG-r15        | 7.1%        | 0.724 |
| Kim DK et al. [60], 2018 | South Korea    | 73         | Mixed    | PHFL                     | 18        | ICG-PDR        | N/A         | 0.748 |
| Wang et al. [61], 2019 | China          | 35         | Mixed    | Day 1-3-5                 | 16        | ICG-r15        | 13.8% (day 1) | 0.540 |
|               |                 |            |          |                          |           |                | 13.8% (day 3) | 0.800 |
|               |                 |            |          |                          |           |                | 22.7% (day 5) | 0.910 |

ICG: Clearance of Indocyanine green; ICG-r15: ICG 15 min retention test; FRL-kICG: ICG constant fraction of future remnant liver; ICG-PDR: ICG-plasma disappearance rate; hep: hepatectomy; HBV: hepatitis B virus; N/A: not available; PHLF: post-hepatectomy liver failure

ICG: Clearance of Indocyanine green; ICG-r15: ICG 15 min retention test; FRL-kICG: ICG constant fraction of future remnant liver; ICG-PDR: ICG-plasma disappearance rate; hep: hepatectomy; HBV: hepatitis B virus; N/A: not available; PHLF: post-hepatectomy liver failure
correlated with the degree of portal hypertension and, since it was first proposed, this score has shown good performance in predicting the development of esophageal varices in cirrhotic patients\textsuperscript{[69-71]}. A recent Chinese study\textsuperscript{[72]} evaluated the accuracy of PSR, calculated using platelet count and spleen volume (expressed in mm\textsuperscript{3}), as a diagnostic index for the stage of liver fibrosis in patients with HCC and compared PSR with other currently-used scores. Among patients with severe fibrosis, AUROC was significantly higher for PSR (0.808) than for other NITs, except for APRI (0.739, \(P = 0.215\)). Peng \textit{et al.}\textsuperscript{[12]}, instead, conducted a study on the risk factors for PHLF in which they used, among various markers, a variant of PSR based on spleen stiffness measurement (SSM), instead of the spleen diameter or volume. On multivariate analysis, PSR seemed to be an independent prognostic index for the development of hepatic decompensation (\(P < 0.001\), odds ratio [OR] = 0.622, 95\%CI: 0.493–0.784). The PSR thus represents a promising prognostic index for the post-resection outcome.

\textit{APRI score}\n
The APRI score (aspartate aminotransferase [AST] to platelet ratio index) was introduced in a study by Wai \textit{et al.}\textsuperscript{[73]} and can be calculated using the following formula: \(\text{AST} (\text{U/L}) \times \left[100/(\text{platelet count} \times 10^3/\text{mm}^3)\right]\). It was developed as a non-invasive predictor for progression of fibrosis in patients with chronic viral hepatitis. In 2019, a study by Mai \textit{et al.}\textsuperscript{[74]} found that the APRI score (AUC 0.743, 95\%CI: 0.706-0.780; \(P < 0.001\)) had greater accuracy for predicting PHLF than the Child-Pugh, MELD and ALBI scores in the entire cohort of patients with HCC. The APRI-score cut-off value of 0.55 was able to reach a sensitivity of 72.2\% and a specificity of 68.0\% on PHLF prediction. However, Zhang \textit{et al.}\textsuperscript{[24]} observed that the APRI score showed a predictive significance only in the major hepatectomy subgroup. The Chinese group of Mai \textit{et al.}\textsuperscript{[45]} used a new combination of ALBI and APRI scores with the following formula: \(\text{ALBI-APRI} = 5.280 \times \text{ALBI} + 1.583 \times \text{APRI}\). The AUC of the ALBI-APRI model (AUC 0.766, 95\%CI: 0.739-0.791) for predicting the risk of PHLF was significantly higher than the single ALBI (\(P < 0.001\)) or APRI scores (\(P = 0.047\)). The ALBI-APRI score cut-off value of -13.10 had a sensitivity of 78.1\% and a specificity of 62.2\% for predicting the risk of PHLF\textsuperscript{[45]}. Thus, the APRI score in combination with other NITs could represent a good surrogate of portal hypertension and should be further investigated for predicting PHLF.

\textit{LSPS}\n
The LSPS (LSM-spleen to platelet ratio score) is a biochemical index derived from the following formula: \(\text{LSM} (\text{kPa}) \times \left[\text{spleen diameter} \times \text{platelet count (10}\text{\(^3/\text{mm}^3)\right]}\). This score was first proposed as a predictive tool for high-risk esophageal varices in patients with HBV-related cirrhosis\textsuperscript{[75]}. In a study by Chon and colleagues\textsuperscript{[76]}, LSPS was found to be an independent risk factor for both HCC (HR = 1.001) and hepatic decompensation (HR = 1.002) in patients with HBV-related hepatitis. Only a single report on 38 patients highlighted a potential predictive role of LSPS on univariate analysis\textsuperscript{[77]}. However, not much is known about the role of LSPS in predicting PHLF.

\textit{Other liver function tests}\n
Over time, other tests for estimating liver function have been developed. These tests use different substrates such as lidocaine, galactose, aminopyrine, amino acid, and methacetin. However, none have been shown to be superior to the ICG clearance test in the prediction of PHLF\textsuperscript{[55]}. Other tests are based on the liver’s energy production (arterial ketone body ratio; AKBR) and the number of receptors for asialo-glycoprotein (ASGP-R; technetium-99m-galactosyl human serum albumin; 99mTc-GSA scan) but they are expensive and less common than ICG\textsuperscript{[25]}. Of course, in the pre-operative assessment, other well-validated tools such as the Child-Pugh and MELD scores continue to be considered. Both have been used widely to predict the outcomes of cirrhotic patients in many different contexts; they showed similar prognostic significance in most cases, even with slight differences in accuracy due to specific settings, as described in a recent, comprehensive meta-analysis\textsuperscript{[78]}. However, as described above, nowadays several NITs (such as FIB-4\textsuperscript{[23]}, APRI score\textsuperscript{[74]}, ALBI score\textsuperscript{[37,39,41,42]} or ICG-r15\textsuperscript{[8]} appear to be better predictors of PHLF, and warrant further study.
Liver stiffness measurement

In the last few years, the liver stiffness measurement (LSM) has been proposed as a practical and widely validated surrogate of liver fibrosis and portal hypertension, able to accurately predict the risk of cirrhosis, CSPH, and its complications, such as the development of varices and hepatic decompensation. Given that these attributes are major determinants of the risk of PHLF development, LSM has been investigated as a predictor of decompensation and other complications after hepatic resection with several methods that are mainly ultrasound-based. The study by Cescon et al. was one of the first papers to demonstrate that LSM, evaluated by transient elastography (TE), was an independent predictor of PHLF, together with histological cirrhosis and lower sodium levels. Since then, numerous studies have confirmed that LSM by TE is an important prognostic preoperative variable that is able to stratify the risk of decompensation, PHLF and overall complications after liver resection. Different cut-offs have been proposed for this purpose, ranging from 9.7 to 22 kPa, which correspond to current cut-offs for advanced chronic liver disease and CSPH. Positive findings have also been described for LSM evaluated by other elastography techniques. For instance, Hu et al. developed and validated a nomogram including LSM assessment by shear-wave elastography, which is able to accurately predict the risk of any grade of PHLF (c-statistic 0.825). More recently, Sato et al. reported in a series of 96 consecutive patients who underwent liver resection, that LSM by magnetic resonance elastography (MRE), with a best-cut-off of 4.3 kPa, was an independent predictor of major surgical complications. When compared to other indices of portal hypertension, the accuracy of LSM was found to be non-inferior to that of the gold standard, hepatic venous pressure gradient (HVPG), and superior to that of ICG-r15. Some preliminary studies have reported a promising role of the spleen stiffness measurement (SSM), which is known to be a more accurate surrogate of portal hypertension but its prognostic role and accuracy in this context have yet to be established.

**Table 3. Studies evaluating LSM by elastography in predicting PHLF**

| Authors          | Country     | Population | Etiology | Outcome     | Nr. cases | Technique | LSM cut-off | AUROC |
|------------------|-------------|------------|----------|-------------|-----------|-----------|-------------|-------|
| Kim et al.       | South Korea | 72         | HCV      | PHLF        | 7         | TE        | 25.6 kPa    | 0.824 |
| Cescon et al.    | Italy       | 90         | HCV      | PHLF        | 26        | TE        | 15.7 kPa    | 0.865 |
| Harada et al.    | Japan       | 50         | HCV      | Ascites     | 19        | ARFI      | 1.6 m/s     | 0.900 |
| Wong et al.      | China       | 105        | HBV      | Major complications | 15 | TE | 12 kPa | 0.790 |
| Zhang et al.     | China       | 75         | HBV      | Ascites     | 13        | TE        | 15.6 kPa    | 0.902 |
| Nishio et al.    | Japan       | 177        | Mixed    | PHLF B or C | 21 | ARFI | 1.61 m/s | 0.780 |
| Cucchetti et al. | Italy       | 202        | 64% HCV  | PHLF        | 60        | TE        | N/A         | N/A   |
| Chong et al.     | China       | 255        | 82% HBV  | PHLF B or C | 46 | TE | 11.5 kPa | 0.650 |
| Han et al.       | China       | 77         | 90% HBV  | PHLF        | 27        | 2D-SWE    | 6.9 kPa    | 0.843 |
| Abe et al.       | Japan       | 175        | Mixed    | Major complications | 28 | MRE | 5.3 kPa | 0.810 |
| Shen et al.      | China       | 280        | HBV      | PHLF        | 55        | 2D-SWE    | 11.8 kPa | 0.720 |
| Rajakannu et al. | France      | 106        | Mixed    | Decompensation | 9  | TE | 22 kPa | 0.810 |
| Donadon et al.   | Italy       | 340        | Mixed    | Complications | 95 | TE | 9.7 kPa | 0.728 |
| Wu et al.        | China       | 54         | 65% HBV  | PHLF        | 7         | TE        | 16.2 kPa    | 0.760 |
| Lei et al.       | China       | 247        | HBV      | PHLF        | 37        | TE        | 14 kPa     | 0.860 |
| Hu et al.        | China       | 216        | 88% HBV  | PHLF        | 64        | SWE       | N/A         | 0.850 |
| Sato et al.      | Japan       | 96         | Mixed    | Major complications | 13 | MRE | 4.3 kPa | 0.813 |
| Procopet et al.  | Romania     | 51         | 65% viral| Decompensation | 15 | TE | 13.6/21 kPa | 0.780 |

ARFI: Acoustic radiation force impulse; HBV: hepatitis B virus; HCV hepatitis C virus; LSM: liver stiffness measurement; MRE: magnetic resonance elastography; N/A: not available; PHLF: post-hepatectomy liver failure; SWE: Shear wave elastography; TE: transient elastography

ULTRASOUND-BASED AND OTHER IMAGING PREDICTORS

Liver stiffness measurement

In the last few years, the liver stiffness measurement (LSM) has been proposed as a practical and widely validated surrogate of liver fibrosis and portal hypertension, able to accurately predict the risk of cirrhosis, CSPH, and its complications, such as the development of varices and hepatic decompensation. Given that these attributes are major determinants of the risk of PHLF development, LSM has been investigated as a predictor of decompensation and other complications after hepatic resection with several methods that are mainly ultrasound-based. The study by Cescon et al. was one of the first papers to demonstrate that LSM, evaluated by transient elastography (TE), was an independent predictor of PHLF, together with histological cirrhosis and lower sodium levels. Since then, numerous studies have confirmed that LSM by TE is an important prognostic preoperative variable that is able to stratify the risk of decompensation, PHLF and overall complications after liver resection. Different cut-offs have been proposed for this purpose, ranging from 9.7 to 22 kPa, which correspond to current cut-offs for advanced chronic liver disease and CSPH respectively. Positive findings have also been described for LSM evaluated by other elastography techniques. For instance, Hu et al. developed and validated a nomogram including LSM assessment by shear-wave elastography, which is able to accurately predict the risk of any grade of PHLF (c-statistic 0.825). More recently, Sato et al. reported in a series of 96 consecutive patients who underwent liver resection, that LSM by magnetic resonance elastography (MRE), with a best-cut-off of 4.3 kPa, was an independent predictor of major surgical complications. When compared to other indices of portal hypertension, the accuracy of LSM was found to be non-inferior to that of the gold standard, hepatic venous pressure gradient (HVPG), and superior to that of ICG-r15. Some preliminary studies have reported a promising role of the spleen stiffness measurement (SSM), which is known to be a more accurate surrogate of portal hypertension but its prognostic role and accuracy in this context have yet to be established.
All the above-mentioned evidence supports the fact that LSM provides valuable prognostic information in patients undergoing liver resection\textsuperscript{[102]}. Indeed, in the last European guidelines on HCC, LSM was included among the pre-operative tools to assess liver reserve before surgery. However, most of the prognostic models including LSM have not been validated externally, the proposed cut-offs differ among studies and differ too, for the elastosonography technique applied. Therefore, LSM is still not routinely used in pre-operative risk stratification of patients undergoing surgery.

Noteworthy, in none of these studies was age an independent predictor of PHLF. However, a recent paper showed that the risk of PHLF development after right hepatectomy rapidly increased in patients over 75 (incidence 35% > 75 years vs. 7% < 75 years, OR = 8.8, 95%CI: 3.6-21)\textsuperscript{[103]}. Considering that older age is a known risk factor for unreliable LSM measurement\textsuperscript{[104,105]} and that this category of patients might have been underrepresented in the previously published cohorts, future studies are needed to investigate the prognostic role of LSM in elderly patients undergoing liver resection.

\textit{Computed tomography}

Several computed tomography (CT) signatures have been reported in association with PHLF\textsuperscript{[106,107]}. With regard to liver volumetry, this is performed using CT imaging, preferably utilizing the images obtained during the venous phase. Liver volumetry is obtained by contouring the liver boundaries and segments, with semi-automated methods or manually, on dedicated software. PHLF occurrence is closely related to the volume and functional capacity of the remnant liver. Patients with a small future liver remnant (FLR) are at higher risk of developing PHLF. Shoup et al.\textsuperscript{[108]} demonstrated that the remnant liver volume (RLV) correlates with post-operative prothrombin time and bilirubin levels. In their analysis, a RLV < 25% was more predictive of PHLF than the anatomical extent of resection\textsuperscript{[108]}. There is no consensus about "how much is enough" but, in general, a FLR of about 20%-30% has been reported as representing the limit of safety in hepatectomy, in non-cirrhotic livers, by some authors\textsuperscript{[109-112]}.

Remnant liver function, estimated with CT volumetry, is reliable only when liver function is assumed homogeneous in the entire organ\textsuperscript{[113]}. In cirrhotic patients, the small liver volume suggests the severity of cirrhosis and poor function of the liver. Indeed, cirrhotic livers have lower levels of hepatocyte growth factor and slower and less complete regeneration, compared with non-cirrhotic livers\textsuperscript{[114]}. Therefore, in these patients, the hepatectomy-associated risk cannot be accurately determined with volumetry alone. In different published series, the critical minimum FLR for a safe hepatectomy was estimated to be approximately 40% in patients with cirrhosis\textsuperscript{[115,116]}.

Spleen Volume (Sp) can also be a critical factor for the outcome of patients undergoing major liver resection. An increased Sp/RLV ratio (> 0.199) correlates with PHLF\textsuperscript{[114]}.

Another imaging pre-operative evaluation that should be assessed is the quantification of hepatic steatosis, which is shown on pre-contrast CT images as lower attenuation of the liver than that of the spleen\textsuperscript{[117]}. Steatosis contributes to post-operative liver dysfunction, especially in diabetic patients and in patients with chemotherapy-associated steatohepatitis undergoing major hepatic resection\textsuperscript{[117]}. The effect of steatosis is explained by the higher incidence of ischemia-reperfusion injury due to altered sinusoidal microcirculation. A recent study found a significantly higher incidence of hepatic decompensation, 90-day post-operative morbidity and surgical hepatic complications in patients with steatohepatitis than in patients without\textsuperscript{[118]}.

Among other conditions that could be associated with older age and contribute to the development of PHLF, it is widely known that primary sarcopenia is strongly associated with age. Therefore, elderly patients have less skeletal muscle mass than younger patients\textsuperscript{[119,120]} and this loss of muscle mass is accelerated due to chronic medical illnesses and malnutrition\textsuperscript{[111]}. At the same time, nutritional status is a major concern.
in liver disease. Cirrhotic patients often develop protein-energy malnutrition (PEM), as a result of poor dietary intake, malabsorption, increased intestinal protein loss, decreased hepatic protein synthesis, abnormal substrate utilization and hypermetabolism. Malnutrition in liver disease is also associated with worse outcomes, increased complications and mortality, and leads to a high prevalence of secondary sarcopenia.

Muscular mass can be evaluated by CT, using different methods such as calculating the area (cm²) and density of the psoas muscle at the level of the third lumbar vertebrae, or calculating the ratio between the muscular surface area (external and internal oblique, transverse, psoas and paravertebral muscles) and the square of height. Recent studies have investigated the effect of sarcopenia on the morbidity of patients undergoing liver surgery, both in cases of colon cancer metastases and of HCC. They have shown that sarcopenia is an independent risk factor for increased post-operative morbidity. Indeed, sarcopenia is associated with a lower functional liver reserve; therefore, the average RLV of sarcopenic patients is statistically and significantly less than that of non-sarcopenic patients. Obese patients can also be sarcopenic if they have increased fatty mass (BMI ≥ 30) but a loss of muscular mass. Peng et al. showed that sarcopenic obesity multiplied the risk of major complications five-fold after hepatectomy in patients with liver metastases.

In addition, on CT, it is possible to calculate the intra-muscular adipose tissue content (IMAC) at the level of L3 (i.e., IMAC = CT attenuation value of the multifidus muscles [HU]/CT attenuation value of the subcutaneous fat [HU]). A recent paper demonstrated that muscle steatosis is associated with significantly lower overall survival and recurrence-free survival, and it is an independent risk factor for increased major post-operative complications in patients undergoing hepatectomy for HCC. Moreover, patients with high IMAC are older and have a higher mass index.

Another comorbidity parameter that can be evaluated with pre-operative CT scan is the bone mineral density (BMD), which is classically defined as a “T-score”, evaluated by dual X-ray absorptiometry (DXA) of the spine or hip. Of note, BMD has a significant negative correlation with age, especially in female patients. Sharma et al. reported BMD by measuring the CT attenuation of the trabecular bone of the eleventh thoracic vertebral body and found that BMD < 160HU was an independent predictor of post-liver transplant mortality in HCC patients. Miyachi et al. demonstrated however, that low BMD (< 160 HU) has a strong correlation with a poor outcome post-hepatectomy only for male patients. Thus, it is possible to utilize peri-operative imaging parameters to assess the future liver remnant and the remnant liver volume, which are strictly correlated with the risk of PHLF; other imaging parameters associated with both the elderly and the health status of the patient, such as the presence of sarcopenia and low bone mineral density, are also associated with PHLF.

Magnetic resonance imaging
Both CT and magnetic resonance imaging (MRI) show excellent accuracy and quantification of hepatic volume. Volumetry assessment by MRI is preferable to be performed on the hepatobiliary phase (HBP, about 30 min after hepatospecific contrast agent injection). Diffusion Weighted Imaging (DWI) measures the apparent diffusion coefficient (ADC) of water, a parameter that is dependent on tissue structure. Several reports suggest a lower ADC value in cirrhosis than in normal livers, probably due to the restricted water diffusion in fibrotic tissue. Chuang et al. reported that pre-operative liver ADC values ≤ 1.34 × 10⁻³ significantly predicted PHLF in patients undergoing hepatectomy.

The administration of hepatospecific contrast agents can help the radiologist and the clinician to evaluate the liver’s reserve function and thus, predicts the occurrence of PHLF. Gadolinium, Gd-EOB-DTPA is a hepato-
specific contrast agent that shows up to 50% hepatocyte uptake and is then excreted into the bile ducts. In non-cirrhotic livers, it has peak enhancement on T1-W images at about 20-30 min after injection.\(^{138,139}\) Uptake and metabolism of this contrast agent is related to hepatocyte function.\(^{140,141}\) Therefore, hepatic parenchymal enhancement is affected by the severity of cirrhosis.\(^{138}\) The mean signal intensity (SI) of liver parenchyma on HBP reflects a quantitative measure of hepatocyte contrast agent uptake.\(^{114}\) Watanabe et al.\(^{142}\) found that liver SI on Gd-EOB-DTPA MRI is strongly correlated with fibrosis stage and concluded that it is more reliable for staging hepatic fibrosis than DWI or hematologic and clinical parameters. Moreover, many recent studies\(^{142,143}\) have reported the usefulness of relative liver enhancement \([\text{RLE} = (\text{SI}_{\text{HBP}} - \text{SI}_{\text{PRE}})/\text{SI}_{\text{PRE}}]\) in predicting PHLF in patients with hepatic metastases or with HCC because of the superiority of pre-operative RLE over both the 50-50 criteria and ISGLS grading system.\(^{67,143}\) Pre-operative RLE measurement is considered reliable and reproducible with high inter-observer variability.\(^{145}\) However, further studies are necessary to understand the real role of RLE to predict PHLF.

Other parameters derived from Gd-EOB-DTPA MRI have been evaluated as predictors of PHLF with modest success. Contrast enhancement ratio \((\text{CER} = [(\text{SI}_{\text{HBP}} - \text{SI}_{\text{PRE}})/(\text{SI}_{\text{TIP}} - \text{SI}_{\text{PRE}})]\) where \(\text{SI}_{\text{TIP}}\) is measured on transitional phases, about 3 min post-contrast injection) is less affected by the hemodynamics of a patient than RLE, and better reflects Gd-EOB-DTPA uptake by hepatocytes. CER can also be multiplied by TLV/SLV ratio (total CER, tCER) and by RLV/SLV ratio (remnant CER, rCER).\(^{114}\) A recent study demonstrated that tCER correlates with the development of PHLF better than volumetry (cut off ≤ 1.23) and that tCER is an independent predictive factor for PHLF (cut off ≤ 1.42).\(^{114}\) The prognostic value of CER, in predicting PHLF, seems to be stronger than the ADC value and TVL/SLV ratio in cirrhotic patients.\(^{114}\) Therefore, patients with a relatively small tCER should preferably go under local treatment rather than resection.\(^{114}\) Asenbaum et al.\(^{146}\) combined functional and morphological parameters (functional FLR, functFLR) by measuring remnant RLE on Gd-EOB-DTPA MRI and the RLV by the formula: (RLV*remnantRLE)/body weight (BW). A decreased functFLR (< 8.73 mL/kg) demonstrated a strong correlation with the development of PHLF in patients that underwent major liver resection.\(^{146}\)

Kim et al.\(^{67}\) verified the correlation between the remnant hepatocellular uptake index \((r\text{HUI} = \text{RLV} \times [(L20/ S20)-1])\) and PHLF, where \(L20\) is the mean SI of the FLR, and \(S20\) is the mean SI of the spleen on HBP images. A lower \(r\text{HUI} < 0.89\) and a lower body weighted and corrected \(r\text{HUI} \text{(rHUI-BW} < 12.38)\) showed a statistically significant correlation with the development of PHLF in patients undergoing major liver resection, and predicted PHLF better than ICG related parameters. In this study, the severity of PHLF also showed a statistically significant association with \(r\text{HUI-BW}\). Nevertheless, despite numerous promising findings, MRI still represents an expensive, not immediate and not widely available technique, and careful evaluation about its use needs to be performed according to each hospital setting. Thus, pre-operative MRI parameters could be useful in predicting PHLF when available, otherwise, cheaper and faster techniques should be used.

**Single photon emission computed tomography**

Single photon emission computed tomography (SPECT) using 99 metastable technetium diethylenetriamine-pentaacetic acid-galactosyl human serum albumin (99mTc-GSA) is of increasing interest for the pre-operative evaluation of cirrhotic patients. The molecule 99mTc-GSA is taken up rapidly by the liver, reflecting accurately the volume of functional liver and FLR; indeed, it is correlated to bilirubin levels, INR, and ICG clearance.\(^{147}\) Liver 99mTc-GSA SPECT has been reported to be more useful than CT in predicting remnant liver function before hepatic resection.\(^{148}\) This technique is thought to be a substitute for ICG rate. It can be used for patients whose liver function cannot be fully estimated using multimodal algorithms, such as patients with jaundice, portal hypertension, or ICG intolerance.\(^{149}\) However, as for MRI, there has not been real-life application of this technique for predicting PHLF to date.
**Interventional radiology**

Portal vein embolization (PVE) is an interventional radiological procedure. It consists of embolization of portal branches in the future resected liver, thus shifting blood flow to the FLR, allowing its hypertrophy before major hepatectomy. By increasing the volume of FLR, the risk for PHLF is decreased, even after extended liver resection\(^{[117]}\). Furthermore, preoperative PVE reduces intra-operative hepatocyte injury caused by the sudden increase in portal pressure at resection. Current guidelines recommend PVE for cirrhotic patients and an estimated FLR of \(\leq 40\%\), or normal patients with an intended FLR of \(<20\%\)^{[150]}. CT volumetry should be performed 3-4 weeks after PVE to assess the degree of hypertrophy, which if \(>5\%\), is associated with improved patient outcomes\(^{[115]}\). A study by Capussotti et al.\(^{[151]}\) reported a FLR hypertrophy of 30%-40% in 4-6 weeks in more than 80% of patients, and was therefore able to prepare patients for hepatectomy after that period. Hepatic arterial buffer response, after reduction of portal blood flow post-PVE, can increase the size of the tumor. However, PVE preceded by trans-arterial chemoembolization (TACE) may prevent this by causing tumour necrosis\(^{[153]}\). RLE on Gd-EOB-DTPA-MRI has also been evaluated both pre- and post-PVE. In particular, the corresponding increase in RLE of the remnant liver at 14 and 28 days after PVE is significantly lower in patients who develop PHLF than in those who do not. Similar results were found comparing patients without or with mild PHLF versus those with severe PHLF\(^{[67]}\).

**CONCLUSION**

PHLF is still an event associated with major concerns by surgeons, especially in elderly patients. Several attempts have been made to identify the best non-invasive predictor of PHLF, in order to introduce a pre-operative tool for the assessment of such risk in routine clinical practice. Particularly, and when available, imaging parameters allow the identification of peri-operative risk factors related to the underlying cirrhosis, the volume of the liver remnant and patient related characteristics, mainly associated with the elderly such as sarcopenia and low bone mineral density. Otherwise, in other settings, LSM as well as ICG-r15 and the ALBI score are useful NITs able to mirror hepatic dysfunction and portal hypertension, and are thus being recommended before surgery for PHLF risk assessment. However, there is still poor evidence for their application in older patients. Further prospective and well-designed studies evaluating the ability of these NITs in predicting PHLF in the elderly are thus needed.

**DECLARATIONS**

**Authors’ contributions**

Conceptualized and designed the review: Marasco G, Colecchia A
Wrote, reviewed and edited the manuscript: Marasco G, Milandri M, Rossini B, Alemanni LV, Dajti E, Ravaioli F
Provided the tables: Alemanni LV, Dajti E
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Read and approved the final manuscript: All authors

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