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REVIEW ARTICLE

Hepatic function assessment to predict post-hepatectomy liver failure: what can we trust? A systematic review

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Abstract

Post hepatectomy liver failure (PHLF) could occur even though an adequate liver volume is preserved. Liver function is not strictly related to the volume and the necessity to pre-operatively predict the future liver remnant (FLR) function is emerging, together with the wide spreading of techniques, aiming to optimize the FLR. The aim of this study was to systematically review all the available tests, to pre-operatively assess the liver function and to estimate the risk of PHLF. A systematic literature research of Medline, Embase, Scopus was performed in accordance to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, to identify all the studies available for pre-operative liver function tests to assess the risk of PHLF and/or complications. From the 1122 references retrieved, 79 were included in the review. Dynamic functional tests, such as indocyanine green test (ICG), could evaluate only global liver function, with no definition of functional capacity of the remnant. Magnetic resonance imaging (MRI) with liver-specific contrast agents enables both liver function and volume evaluation; the absence of ionizing radiation showed a better patient's compliance. Nuclear imaging studies as hepatobiliary scintigraphy (HBS) present the unique ability to allow a precise evaluation of the segmental liver function of the remnant liver. Liver volume could overestimate liver function. Several liver function tests are available to evaluate the risk of PHLF in the pre-operative setting. However, no single test alone could accurately predict PHLF. Pre-operative combination between a dynamic quantitative test, such as ICG, with MRI or HBS, should enable a more complete functional evaluation. Functional tests to predict PHLF should be chosen according to patient's characteristics, disease, and center experience.

Keywords Hepatic function · Liver resection · Liver surgery · Hepatectomy · Post-hepatectomy liver failure

Introduction

The improvements in the surgical techniques, together with targeted chemotherapy treatments, have increased the resectability rates in the presence of extensive liver involvement. Staged hepatectomies, such as Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS), in combination or following portal vein embolization (PVE), enable extended resections in patients with massive liver involvement by inducing hypertrophy of the future liver remnant (FLR). These procedures, however, expose patients to the risk of post hepatectomy liver failure (PHLF), especially in those with non-tumoral liver parenchyma compromised by chemotherapy toxicity, steatosis, fibrosis, or cholestasis.

Preoperative evaluation of the FLR is therefore crucial to determine whether an extended liver resection could be safely performed. In Western countries, this evaluation mainly relies on the volumetric assessment of the FLR based on computed tomography (CT) or magnetic resonance imaging (MRI). However, recent studies demonstrated that liver function is not necessarily related to liver volume and that PHLF could occur even though an adequate FLR volume is preserved [1–4].

On this background, several hepatobiliary centers have introduced in the preoperative work-out, the functional evaluation of the FLR, particularly during staged-hepatectomies.

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To date, several laboratory tests and radiologic examinations have been developed to evaluate liver function. The ideal test should be accurate in predicting the outcomes, easy to perform, cost-efficient, and reproducible to allow inter-centers comparisons.

The aim of this systematic review is to describe and discuss the tests currently available in the clinical setting of pre-operative evaluation of liver function and the risk assessment of PHLF.

Methods

Search strategy and study selection

This systematic review was performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [5]. An electronic search of Medline, Embase, Scopus, and the Cochrane collaboration databases was performed up to June 2019. For Medline, the following combination of search terms was used: "(liver OR hepatic) AND function AND (hepatectomy OR liver resection) AND liver failure". The same keywords were similarly combined into the search fields of other databases.

Two reviewers (F.T and M.C.G.) independently screened the results of the electronic search at the title and abstract level and the full-text of potentially eligible studies was retrieved for further analysis. References of relevant publications were screened to identify additional studies of interest.

Only the human studies published in English were considered. To be included, the studies had to evaluate one or more methods to assess liver function before liver resection (including living donation of right or left liver lobe) and to predict PHLF and/or postoperative complications.

Studies were excluded in cases as follows: (1) focused on liver transplantation; (2) focused on liver volumetric evaluation alone; (3) evaluated only laboratory tests or grading system or scores based exclusively on laboratory test values; (4) outcomes of interest were not reported; (5) methodology was not clearly reported. In the case of multiple studies from the same group with overlapping data and results, the largest or the most recent was included in the review.

Data extraction

The following data were extracted from the selected studies: title and reference details (first author, journal, year, country), the methodology employed for liver function assessment, study population characteristics (number of patients, type of the study) and clinical outcomes of interest. All the data were recorded independently by both literature reviewers and then compared to limit selection bias. Any divergence was solved by discussion.

Results

From the 1122 references retrieved, 165 were identified at the title or abstract level. After the evaluation of the manuscript's full-text, 79 studies were included in the review (Fig. 1, PRISMA diagram).

Six function tests were identified, which could be classified as dynamic liver function tests and imaging-based function tests. Tests should also be classified as evaluating: (1) global liver function as indocyanine green (ICG) clearance, LiMAx and monoethylglycinexylidide (MEGX); (2) segmental function as magnetic resonance (MRI) and hepatobiliary scintigraphy (HBS). In particular, dynamic liver function tests assess the global liver function and metabolic reserve, by monitoring the hepatic metabolism of an administered exogenous substance, whose blood levels could be easily measured [6–8]. These tests do not provide information about FLR function, which could only be supposed on the basis of FLR volume, calculated by the additional use of CT-volumetry, given the assumption that liver function is homogenous within the liver. Conversely, imaging-based tests provide information regarding both actual total and segmental liver function [9–12].

Dynamic liver function tests

The indocyanine green (ICG) clearance

The ICG clearance test is a widely used liver function test, more frequently in the Eastern [13–22] than in the Western world [23–28].

ICG is a fluorescent dye that is selectively uptaken by the liver and eliminated through the bile. Following ICG intravenous (I.V.) injection of 0.5 mg/kg, healthy livers excrete 97% of the dye in about 20 min. The ICG clearance can be determined as peri- or intra-operative by serum sampling or pulse dye densitometry using an optical transcutaneous sensor [15, 25, 29–32].

ICG clearance is reported as ICG percentage retained after 15 min (ICG-R15) [8, 13, 16, 18, 20, 21, 26, 33], or as ICG plasma disappearance rate (ICG-PDR) per min, [6, 8, 27, 29, 30, 34] (Table 1). ICG-R15 $\leq$ 15% and ICG-PDR $\geq$ 18%/min after 15 min are usually found in healthy livers. However, worse ICG-R15 or ICG-PDR values indicated higher risk of PHLF depending on the extent of liver resection [19, 35].

ICG accuracy in predicting PHLF, hepatic decompensation, (i.e., 3-month postoperative ascites, impaired quality of life and survival) and mortality has been confirmed in patients with cirrhosis and HCC [23, 36, 37], as well as for peri-hilar cholangiocarcinoma [23, 34]. Conversely,

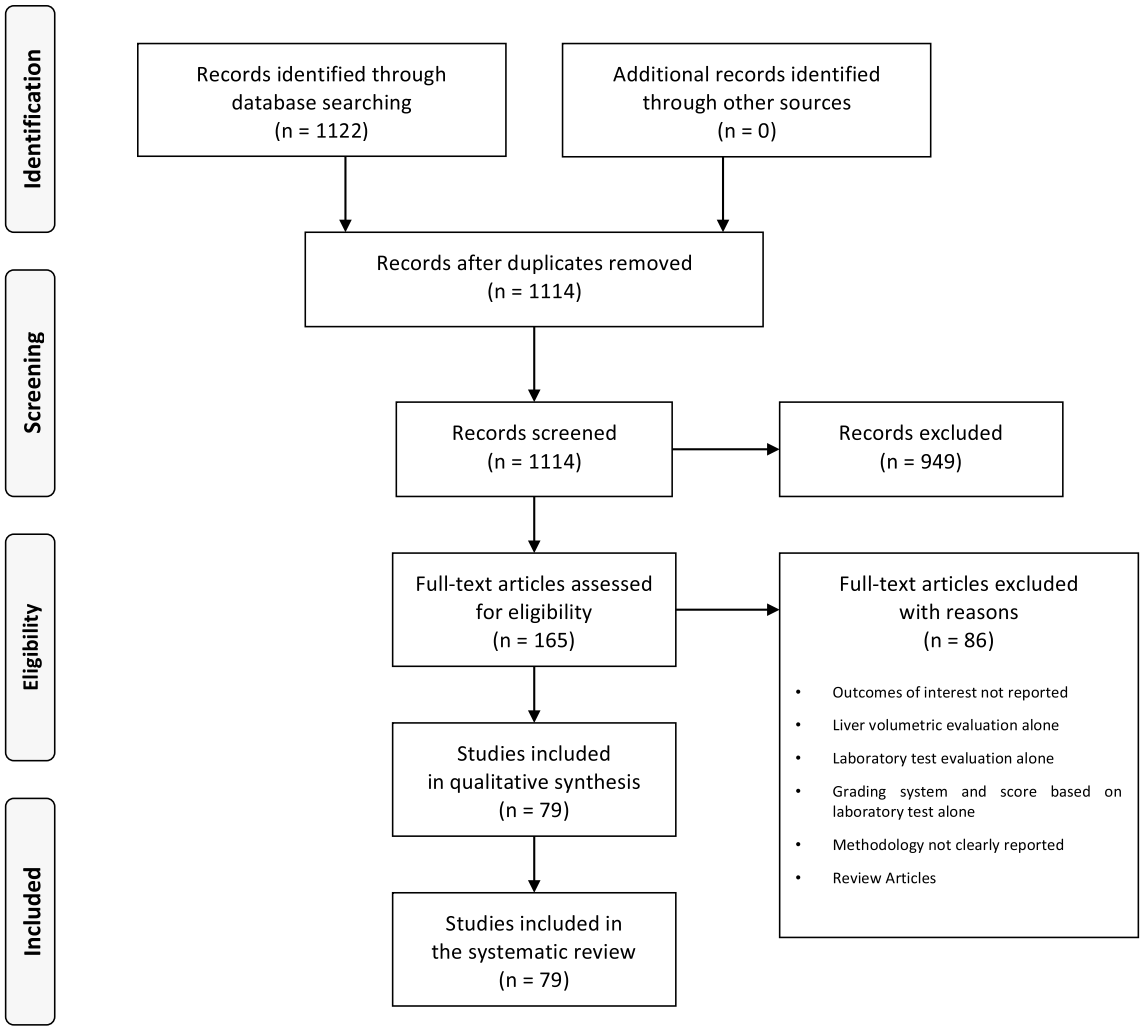

Fig. 1 Study flow diagram

ICG has low-accuracy in predicting PHLF in non-cirrhotic patients [24]. Therefore, this test should be reserved for patients with cirrhosis [18, 24, 26, 33, 38].

The ICG clearance of the FLR could also be estimated by combining ICG clearance data with FLR volume [34, 37–40]. ICG clearance values of the FLR > 0.04 and 0.05 have been shown to accurately predict PHLF in patients undergoing major resection of normal and diseased liver, respectively [37, 40]. ICG clearance rate of the FLR is also able to predict, better than liver volume, the occurrence of PHFL after PVE [39].

Regarding the reliability, it is important to underline that ICG clearance depends on liver blood flow and bile secretion. Therefore, vascular factors (e.g., thrombosis, arterial shunt and portal hypertension) and biliary obstruction alter the test result [6, 7, 41, 42].

The albumin-indocyanine green evaluation (ALICE) grading system

Albumin-indocyanine green evaluation (ALICE) is a grading system for patients with liver cirrhosis and hepatocellular carcinoma (HCC) [43] which combines serum albumin levels and ICG-R15 values, according to the formula: $0.663 \times \log_{10}$ (ICG-R15 [%])-$0.0718 \times$ albumin (g/L). Multiple studies have confirmed the ability of ALICE to predict PHLF and mortality in patients, undergoing major liver resection for HCC, by stratifying patients into three classes of risk [43–45]. ALICE has also been validated in patients with biliary tract cancer [45]. Particularly, ALICE > − 1.88 was noted as a risk factor for PHLF [45].

Table 1 Selected studies evaluating ICG and ALICE

Author and year of publication	*n*	Type of study	PHLF definition	Liver disease**	Main findings
ICG test					
Mizumoto et al. 1979 [22]	76	R	Clinical*	47%	Worst outcomes with lower ICG max removal rate
Okamoto et al. 1984 [21]	38	R	Clinical	74%	ICG-R15 in related to parenchymal resection and outcomes
Zoedler et al. 1995 [28]	20	R	Clinical	50%	ICG predict PHLF
Lau et al. 1997 [20]	127	R	Clinical	Not report	ICG-R15 is the best predictor for post-op. mortality
Lam et al. 1999 [18]	117	R	Clinical	82%	In low ICG, major hepatectomy can be performed reducing intra-operative blood loss
Torzilli et al. 1999 [19]	107	R	Clinical	93.5%	ICG-R15 help to evaluate the risk of liver resection for HCC
Okochi et al. 2002 [32]	22	R	Clinical	50%	ICG predict morbidity
Wakabayashy et al. 2002 [16]	45	R	Clinical	Not report	Post-PVE ICG-R15 > 16% increase the risk of PHLF
Sugimoto et al. 2006 [15]	51	P	Clinical	29%	ICG can early predict PHLF
Scheingraber et al. 2008 [27]	96	P	Clinical	10%	ICG plasma disappearance rate predict liver dysfunction
de Liguori Carino et al. 2009 [29]	37	R	Clinical	None	ICG plasma disappearance rate for early PHLF detection
Yokoyama et al. 2010 [37]	274	R	Clinical	Not report	ICG of FLR < 0.05 for post. op. mortality
Greco et al. 2011 [26]	129	R	MELD	63%	Elevated ICG-R15 associated with PHLF and morbidity
Ren et al. 2012 [13]	144	R/CS	Clinical	14%	ICG-R15 predict PHLF in hepatolithiasis better than CP
Derpapas et al. 2013 [25]	31	R	Clinical	35%	ICG reduce risk of PHLF
Thomas et al. 2015 [30]	20	R	ISGLS	Not report	ICG correlates with PHLF risk
Hwang et al. 2015 [40]	723	R	Clinical	80%	ICG of FLR cut-off of < 0.05 for PHLF
Kim et al. 2015 [38]	81	R	Clinical + 50–50	47%	IGG-R15 correlate with safety for major hepatectomy
Kambakamba et al. 2016 [33]	36	R	ISGLS + 50–50	None	ICG-R15 increase in PHLF after ALPPS
Yokoyama et al. 2016 [34]	585	R	ISGLS	Not report	ICG of the FLR predict PHLF in major hepatectomy
Ibis et al. 2017 [24]	53	R	ISGLS	None	Not predictive of PHLF in non-cirrhotic patients
Le Roy et al. 2018 [23]	147	M	ISGLS + 50–50	56%	ICG-R15 > 15% predict hepatic decompensation
Maruyama et al. 2018 [39]	20	R	ISGLS	None	ICG of FLR is related with PHLF and is more accurate that volume
Wang et al 2018 [36]	185	R	ISGLS	73%	ICG-R15 is more accurate than MELD and CP in predict hepatic reserve and PHLF
ALICE					
Kokudo et al. 2016 [43]	70	P	Clinical	Not report	ALICE grade allow better prediction of PHLF and mortality
Miyazaky et al. 2018 [45]	166	R	ISGLS + 50–50 + Mullen's	Not report	ALICE > -1.88 as independent risk factors for PHLF
Russolillo et al. 2018 [44]	400	M	ISGLS	100%	The incidence of ascites and PHLF increase with ALICE grade

R retrospective, *P* prospective, *R/CS* retrospective case control, *M* multicenter

CP Child Pugh, *MELD* model for end-stage liver disease, *ISGLS* International Study Group of Liver Surgery; 50–50 criteria

*Defined by laboratory test (bilirubin, INR, albumin, AST, ALT) and/or clinical course (ascites, encephalopathy, death) without following any classification

**Defined as percentage (%) of cases with cirrhosis, chemotherapy steato-hepatitis, jaundice and viral chronic hepatitis

The LiMAx test

The LiMAx test evaluates the hepatic metabolism of the ^{13}C-labelled substrate (methacetin; Euriso-top, Saint-AubinCedex, France) [46, 47]. After I.V. injection, the ^{13}C-methacetin is rapidly metabolized into acetaminophen and the demethylated ^{13}C-group is converted into $^{13}CO_2$, which is exhaled. This determines an alteration of the normal $^{13}CO_2/^{12}CO_2$ ratio in the exhaled, which is measured by a specific device. Liver function is calculated from the analysis of the variation of the $^{13}CO_2$:$^{12}CO_2$ ratio over 60 min.

Liver resection leads to a decrease of the postoperative LiMAx value, which accurately represents the liver functional reserve [46–49] (Table 2). Particularly, LiMAx test on the first post-operative day lower than 80 µg/kg/h, is associated with PHLF and increased mortality. On these findings, the postoperative FLR function was estimated by associating preoperative LiMax and FLR volume, with patients having LiMAx < 80 µg/kg/h excluded from the immediate surgery [47], resulting in a reduction of postoperative mortality [47].

Regarding the staged procedures, preoperative LiMAx test combined with CT volumetry, enabled a reliable estimation of post-operative liver function after the PVE. However, due to the absence of the liver-related deaths, the analysis of pre-operative LiMAx as a predictor for postoperative mortality was precluded [50].

The monoethylglycinexylidide (MEGX)

The MEGX test evaluates the hepatic conversion (through the cytochrome P450 system) of lidocaine to MEGX [6, 7, 51, 52]. After the I.V. infusion of 1 mg/kg of 2% lidocaine hydrochloride, MEGX rapidly appeares in the plasma, reaches a steady-state in 15 min and its plasma levels could be measured before and at 15, 30 or 60 min, with normal value ranging between 60 and 96 ng/ml [51–53]. As an alternative, serial blood samples can be taken for up to 6 h to calculate the lidocaine half-life [52].

MEGX test predict survival in patients with liver diseases [6, 53] (Table 2) and MEGX levels at 30 min correlate with the development of ascites, PHLF and in-hospital mortality in non-cirrhotic patients [53]. The major limitation for routine clinical use of the MEGX test is the wide inter-individual variability, particularly the inhibitors of the cytochrome P-450 system activity (e.g., erythromycin, ketoconazole), which could alter the results [6].

Imaging-based liver function tests

MRI with liver-specific contrast

In addition to the diagnostic purposes, MRI with liver-specific contrast agents could be used to also measure global and segmental liver function, through the analysis of contrast uptake and excretion. Among the available contrasts, only Gadolinium ethoxybenzyl DTPA (Gd-EOB-DTPA, Primovist®, Bayer AG, Berlin) could be used to evaluate the liver function, since it is specifically absorbed by the hepatocytes. This uptake is mediated by the transmembrane transporters, whose expression or activity is significantly reduced in diseased livers. The relative increase in the signal intensity (SI) of the liver parenchyma between the unenhanced (SI_{un}) and hepatobiliary phase (SI_{hp}) correlates with liver function,

Table 2 Selected studies evaluating LiMAx and MEGX

Author and year of publication	*n*	Type of study	PHLF definition	Liver disease**	Main findings
LiMAx Test					
Stockmann et al. 2009 [46]	64	P	Clinical*	6%	LiMAx at POD 1 as the only predictor for mortality and PHLF
Lock et al. 2009 [49]	48	R	Clinical	Not report	Patients developing PHLF had a lower LiMAx
Stockmann et al. 2010 [47]	329	P	LiMAX	None	Pre-operative LiMAx of the FLR < 80 µg/kg/h increase risk of PHLF
Malinowski et al. 2015 [50]	31	P	Clinical	6.5%	Preoperative LiMAx combined with CT volumetry estimate post-operative liver function after PVE
Lodewick et al. 2017 [48]	59	R	LSCEP	6%	LiMAx not affected by age
MEGX					
Lorf et al. 2008 [53]	55	R	Clinical	100%	Preoperative MEGX-30 correlated with in hospital mortality

R retrospective, *P* prospective, *POD* post-operative day, *LSCEP* liver-specific composite end point

*Defined by laboratory test (bilirubin, INR, albumin, AST, ALT) and/or clinical course (ascites, encephalopathy, death) without following any classification

**Defined as percentage (%) of cases with cirrhosis, chemotherapy steato-hepatitis, jaundice and viral chronic hepatitis

expressed as the relative liver enhancement (RLE), according to the formula: $[(SI_{hp}\text{-}SI_{un})/SI_{un}]$ [11, 54–59].

The selected studies evaluating MRI as a liver function test are reported in Table 3. Wibner et al. showed that patients with lower RLE values presented worse outcomes, with an RLE < 100% significantly associated with PHFL [54]. Moreover, the RLE of the FLR was pointed out as a more accurate parameter than standard liver volumetry and ICG in predicting PHLF [57, 60]. In line with these findings, several studies demonstrated that MRI with Gd-EOB-DTPA could accurately predict PHLF after major liver resection [58, 59, 61].

Moreover, MRI could also predict liver growth following PVE. Particularly, fat-signal-fraction measured at MRI, but not RLE, inversely correlates with the kinetic growth rate of the FLR, with higher values (> 4.9%) associated with a lower FLR growth and higher complication rates [56]. However, low RLE values of the FLR were associated with PHLF following PVE by different authors [55].

Nuclear medicine techniques imaging modalities

Technetium-99 m(^{99}mTc)-labeled diethylenetriaminepentaacetic acid and galactosyl human serum albumin (GSA) scintigraphy

GSA is an asialoglycoproteins analog that binds to the specific receptors on hepatocytes, which are under-expressed in chronic liver diseases [8, 10, 62]. GSA is exclusively absorbed by the liver, where it remains trapped for at least 30 min [6]. Moreover, since the absorption of GSA is not influenced by bilirubin serum levels, ^{99m}Tc-GSA-HBS is reliable even in the presence of cholestasis [7].

After ^{99m}Tc-GSA-HBS I.V. injection, a gamma camera was placed over the heart and liver and regions of interest (ROIs) were generated to calculate the ^{99m}Tc-GSA liver uptake, blood clearance and maximal removal rate, through planar dynamic scintigraphy. ^{99m}Tc-GSA-HBS results correlate with the postoperative outcomes, including PHLF [7, 62–67] (Table 4). However, PHLF occurred in patients showing normal ^{99m}Tc-GSA uptake, probably because ^{99m}Tc-GSA-HBS does not provide information regarding the segmental liver function [7]. For this reason, ^{99m}Tc-GSA scintigraphy is combined with SPECT-CT to provide information about the FLR function, measured as the FLR uptake ratio [7, 10, 68]. This parameter has been found to correlate with the patient's liver functional status (i.e., child-score, presence of ascites and hyperbilirubinemia) and to be a good predictor of postoperative outcomes, including PHLF [69–77] even for two-stage procedures [78–80].

Evaluating the GSA maximal removal rate of the FLR, this parameter strongly correlates with ICG-R15 and post-operative total bilirubin values, predicting the development of long-term ascites [63, 81] and PHLF [67, 82, 83].

Regarding the living donors, Kobayashi et al. reported that mildly impaired post-surgical GSA function did not indicate poor prognosis and careful attention may be only required for donors undergoing larger resection [84].

Hepatobiliary scintigraphy with ^{99m}Tc-labeled iminodiacetic acid (IDA) derivatives—^{99m}Tc-Mebrofenin.

^{99m}Tc-IDA agents are lidocaine analogs which are absorbed by the hepatocytes and excreted into the biliary system without any biotransformation [9, 12]. ^{99m}Tc-mebrofenin is the ^{99m}Tc-IDA derivative [7, 10, 12, 85] with the highest hepatic absorption, minimal urinary excretion and lowest displacement by bilirubin [9, 12]. ^{99m}Tc-mebrofenin-HBS is therefore used to obtain functional imaging of the liver and to evaluate the hepatobiliary system for several biliary diseases [10].

Table 3 Selected studies evaluating the functional liver assessment using Gd-EOB-DTPA – MRI

Author and year of publication	*n*	Type of study	PHLF definition	Liver disease**	Main findings
Cho et al. 2011 [59]	29	R	ISGLS	48%	MRI predict PHLF after major hepatectomy
Wibner et al. 2013 [54]	73	R	ISGLS + 50–50	None	MRI asses the risk of PHLF after major hepatectomy
Sato et al. 2015 [55]	53	R	ISGLS	Not report	MRI was related with PHLF after PVE
Barth et al. 2016 [56]	45	R	ISGLS	44%	Liver fat-content derived from MRI predict FLR-growth and PHLF after portal vein occlusion
Costa et al. 2017 [58]	65	R	ISGLS	13%	Use of MRI improve pre-op risk assessment for PHLF
Yoon et al. 2016 [61]	57	P/M	50–50	52%	Pre-op. MRI showed negative correlation with post-op. ICG-R15
Kim et al. 2018 [60]	73	R	ISGLS	51%	MRI predict PHLF better than ICG for HCC
Asenbaum et al. 2018 [57]	62	R	ISGLS	Not report	MRI is a superior predictive factor for PHLF

R retrospective, *P/M* prospective multicenter, *ISGLS* International Study Group of Liver Surgery; 50–50 criteria

**Defined as percentage (%) of cases with cirrhosis, chemotherapy steato-hepatitis, jaundice and viral chronic hepatitis

Table 4 Selected studies evaluating the functional liver assessment using nuclear medicine technique imaging modalities

Author and year of publication	*n*	Type of study	PHLF definition	Liver disease**	Main findings
99mTc-GSA					
Kwon et al. 1997 [82]	90	P	Clinical*	65%	Pre-op. ^{99m}Tc-GSA maximal removal rate was lower in PHLF
Hwang et al. 1999 [62]	55	R	Clinical	Not report	lower ^{99m}Tc-GSA in PHLF
Kokudo et al. 2002 [66]	111	R	Clinical	39%	^{99m}Tc-GSA uptake of the FLR as predictive factor for PHLF
Nishiyama et al. 2003 [80]	8	P	Clinical	Not report	Higher ^{99m}Tc-GSA present lower probability of PHLF
Kwon et al. 2006 [83]	178	R	Clinical	47%	^{99m}Tc-GSA Removal rate of the FLR was lower in PHLF
Kaibori et al. 2008 [65]	191	P	Clinical	63%	^{99m}Tc-GSA Removal rate of the FLR as only risk factor for PHLF
Nanashima et al. 2010 [64]	250	R	Clinical	25%	^{99m}Tc-GSA reduce the incidence of hepatic complications
Yumoto et al. 2010 [78]	101	R	Clinical	39%	^{99m}Tc- GSA was related with the incidence of PHLF
Tatsumi et al. 2013 [71]	48	R	Clinical	None	In acute liver failure without chronic liver disease, ^{99m}Tc-GSA predict prognosis
Nanashima et al. 2013 [72]	442	R	Clinical	54%	^{99m}Tc- GSA associates with hepatectomy related complication
Yoshida et al. 2014 [68]	95	R	Clinical	27%	^{99m}Tc- GSA uptake predict PHLF
Mao et al. 2015 [69]	142	P	Clinical	48%	^{99m}Tc- GSA uptake predict PHLF
Kobayashi et al. 2015 [84]	74	R	Clinical	None	Mildly impaired ^{99m}Tc- GSA uptake not indicate poor prognosis in living donor
Hayashi et al. 2015 [70]	133	R	ISGLS	19%	^{99m}Tc- GSA uptake is a better predictor of post-op. outcomes
Sumiyoshi et al. 2016 [73]	30	R	ISGLS	None	^{99m}Tc- GSA uptake was lower in PHLF
Okabayashi et al. 2017 [74]	185	P	ISGLS + 50–50	None	^{99m}Tc- GSA uptake correlate with total bilirubin and PT-INR
Yano et al. 2017 [81]	200	R	Clinical	27%	Lower ^{99m}Tc- GSA maximal removal rate was associated with postoperative long-term ascites
Yada et al. 2018 [41]	20	P	Clinical	30% icteric	^{99m}Tc- GSA was important for avoiding PHLF
Sumiyoshi et al. 2018 [75]	13	R	Clinical	30%	^{99m}Tc- GSA enables a more accurate liver function assessment than ICG with no incidence of PHLF in hepatectomy defined pre-operatively safe
Yoshida et al. 2018 [76]	62	R	ISGLS	32%	^{99m}Tc- GSA uptake is correlated with hepatic venous congestion
Mizutani et al. 2018 [67]	136	R	ISGLS	Not report	^{99m}Tc- GSA removal rate predict PHLF
Nakamura et al. 2018 [77]	218	R	ISGLS	Not report	^{99m}Tc- GSA uptake as risk factor for PHLF
Chiba et al. 2018 [79]	27	R	ISGLS	None	Liver hypertrophy after two-stage procedures correlates with initial liver function
Tanoue et al. 2019 [63]	247	R	Clinical	71%	^{99m}Tc- GSA removal rate was lower in long-term ascites
99mTc-Mebrofenin					
Bennink et al. 2004 [1]	15	P	Clinical	None	Good correlation with ICG but not with FLR volume in uncomplicated liver resection
de Graaf et al. 2010 [86]	55	R	Clinical	54%	More accurate than volumetry. Cutoff of 2.7%/min for PHLF
de Graaf et al. 2011 [96]	24	P	Clinical	54%	FLR function increase more than volume after PVE
Chapelle et al. 2016 [91]	88	P	ISGLS	62%	More accurate than volumetry. Cutoff of 2.3%/min for PHLF
Cieslak et al. 2016 [90]	163	R	ISGLS	63%	Reduction of PHLF incidence using pre-op. HBS
Chapelle et al. 2017 [92]	100	P/CS	ISGLS	6%	Validated the previous cut-off of 2.3%/min for PHLF
Truant et al. 2017 [95]	7	P	ISGLS	None	at ALPPS interstage gain in function is lower than volumetric regeneration
Olthof et al. 2017 [4]	116	R	ISGLS	Not report	^{99m}Tc-Mebrofenin better predict risk of PHLF for PHC

Table 4 (continued)

Author and year of publication	*n*	Type of study	PHLF definition	Liver disease**	Main findings
Chapelle et al. 2017 [3]	140	P	ISGLS	30%	^{99m}Tc-Mebrofenin of the FLR better predict PHLF for CRLM
Cieslak et al. 2017 [98]	63	P	Clinical	40%	^{99m}Tc-Mebrofenin predict insufficient hypertrophy after PVE
Olthof et al. 2017 [93]	60	M	ISGLS	Not report	Volumetry overestimates FLR function in ALPPS
Sparrelid et al. 2017 [94]	9	P	ISGLS + 50–50	Not report	Volumetry overestimates FLR function in ALPPS
Serenari et al. 2018 [99]	37	R	ISGLS	None	^{99m}Tc-Mebrofenin predict PHLF in liver resection and in living donation
Truant et al. 2019 [97]	125	P	ISGLS	None	FLR function is related with PHLF better than volume

R retrospective, *P* prospective, *P/CS* prospective case control, *M* multicenter, *ISGLS* International Study Group of Liver Surgery; 50–50 criteria, *PHC* peri-hilar cholangiocarcinoma, *CRLM* colorectal liver metastases

*Defined by laboratory test (bilirubin, INR, albumin, AST, ALT) and/or clinical course (ascites, encephalopathy, death) without following any classification

**Defined as percentage (%) of cases with cirrhosis, viral chronic hepatitis, chemotherapy steato-hepatitis and jaundice

After I.V. injection, the liver ^{99m}Tc-mebrofenin absorption rate is measured by dynamic scintigraphy, with a dual-head gamma camera that measures time-activity curves from ROIs drawn on the heart, the liver, and the total field of view. The ^{99m}Tc-mebrofenin uptake ratio is corrected for the body surface area (%/min/m^2), to take into account the individual metabolic requirements [86]. A three-dimensional SPECT-CT is subsequently performed to evaluate and distinguish the functional from non-functional liver segments, giving visual and functional information [87].

Studies evaluating ^{99m}Tc-mebrofenin HBS as liver function tests are shown in Table 4. ^{99m}Tc-mebrofenin correlates with ICG after liver resection [1, 12, 52, 88], since its absorption, excretion, and lack of hepatic biotransformation are similar [7, 88].

A ^{99m}Tc-mebrofenin uptake of the FLR inferior to 2.69%/min/m^2 has been reported by De Graaf et al. and further validated as a predictor of PHLF, after major liver resection, even for two-stage procedures [86, 89, 90]. However, other studies suggested 2.3%/min/m^2 as cut-off to identify patients that are at higher risk of PHLF [91, 92].

Our study group routinely performs ^{99m}Tc-mebrofenin HBS before major hepatectomies, especially during the pre-operative and inter-stage evaluation of staged procedures, including ALPPS [2, 89]. Several papers suggest that functional evaluation of the FLR with ^{99m}Tc-mebrofenin HBS at ALPPS interstage, is correlated with the risk of PHLF and mortality after the second stage [89, 93–95]. However, due to limited number of events, conclusions could not be clearly defined.

Therefore, pre-operative association between volumetric and functional assessment has to be considered currently as one of the most accurate and reliable methods to predict the risk of PHLF [91, 96, 97]. The possibility to obtain quantitative and visual information on the segmental liver function is, therefore, crucial during the preoperative evaluation of major hepatectomy and two-stage procedures [89, 96–98]. Moreover, ^{99m}Tc-mebrofenin HBS is a non-invasive low-cost exam that could easily be performed [10, 87, 89, 93, 97, 98].^{99m}Tc-mebrofenin HBS has also been tested as predictor of PHLF in living donors [99]. However, larger studies are needed to draw final and robust conclusions regarding its benefits in this setting.

Discussion

Liver volume is not always a reliable predictor of liver function after hepatectomy and additional functional assessment before major hepatic resections is therefore necessary [1, 3, 4, 97]. Despite the presence of a correlation between liver volume and function, a high variability exists, with patients having a considerable increase in the FLR volume but only a modest increase in function [1, 3, 4, 94, 97]. In particular, the volume could overestimate the function following the rapid FLR regeneration, induced by ALPPS [93], where the fast volume increase is not paralleled by a corresponding gain in function [94]. Based on the sole volumetric evaluation, ALPPS stage-2 risks to be performed with the wrong timing, leading to high morbidity and mortality rates.

However, the mismatch between liver function and volume could be observed also in the opposite direction, with liver volume underestimating the function. Indeed, de Graaf et al. showed how after PVE, the increase in FLR function could even appear greater than volumetric regeneration [96].

Therefore, a pre-operative assessment solely based on the changes in liver volume has to be considered as inadequate.

In this setting, several authors proposed to move from a volumetric to functionmetric evaluation [10, 87].

Liver function is related to several different processes, including uptake, synthesis, biotransformation, and excretion. Therefore, a single test cannot evaluate all these processes at the same time. Clinical and radiological evaluations have to work synergistically to estimate more precisely liver functional reserve to decide whether a liver resection could be performed safely.

Different functional tests are available and validated in the literature. However, due to great variability, an accurate evaluation of the pros and cons of each test is crucial to choose the best option (Table 5).

Makuuchi first reported a decisional algorithm based on ICG-R15, ascites, and serum bilirubin level, subsequently validated by other authors [19, 35, 100]. Takasaki also described a mathematical method considering ICG-R15 and extent of hepatectomy to identify the limit to liver resection in cirrhotic and non-cirrhotic patients [101]. Dynamic liver function tests have the advantage of easy administration, reduced cost, and easy repeatability. Moreover, these tests could also be administered intraoperatively, in case unexpected surgical findings could suggest resecting a liver volume larger than that preoperatively planned. The main drawback of ICG-based tests and other dynamic liver function tests (LiMAx and MEGX), is that only global liver function could be evaluated and the functional capacity of FLR cannot be precisely defined. Future remnant liver function could be only hypothesized by correcting global liver function for FLR volume. However, these methods assume a homogenous liver function, which is not always true, especially in case of cholestasis, vascular thrombosis or during the interval period of staged hepatectomies. These limitations are considerable, especially in the modern era while HPB surgeons are pushing the limits of resectability by widely applying the surgical techniques to induce FLR hypertrophy (e.g., ALPPS). Intraoperative evaluation of ICG fluorescence of the FLR represents a possible application to overcome this limit, however data are still limited [102]. Furthermore, compared to a pre-operative test, intraoperative evaluation has a limited impact on surgical planning in patients undergoing a major or two-stage hepatectomy.

MRI is probably the most promising liver function test, in view of its diagnostic value, the possibility to calculate liver volumetry, and the absence of radiation exposure. Ideally, a diagnostic, volumetric and functional assessment could be performed using only one test, thus saving time and reducing costs. However, to date, MRI has been scarcely studied in the surgical literature as a liver function test, especially if compared to HBS, and needs further validation studies. Nuclear imaging studies based on SPECT-CT also provide a simultaneous morphologic (visual) and physiologic (functional) information and could detect functional differences between liver segments, with the possibility of evaluating FLR function. HBS with ^{99m}Tc-mebrofenin seems to be a valuable tool to pre-operatively define FLR function before major and two-stage hepatectomies [2, 93]. Unquestionably, both MRI and HBS need specific competences and logistics, possibly carrying higher costs than non-imaging tests. However, these disadvantages should be weighed against the potential benefits of significantly improving patients' outcomes, which lead to a global cost reduction. Dedicated studies with appropriate cost-effectiveness analysis are therefore needed.

In conclusion, volumetric evaluation needs to be associated with liver function tests to guide surgical decision-making in liver surgery, particularly in the case of staged hepatectomies. Several liver function tests are available and proved their usefulness and accuracy. However, it's difficult to define if a single test alone is capable to predict

Table 5 Pros and cons of the most widely used functional test

Functional test	Pros	Cons
The indocyanine green (ICG)	Easy to perform peri-operatively at patient's bed	Global liver function can be only evaluated
	Performed even intra-operatively	Less accurate in non-cirrhotic patients
	Well established in literature	Necessary additional volumetric evaluation
MRI with Gd-EOB-DTPA	No exposition to ionizing radiation	Specific competence needed
	Simultaneous volumetric evaluation possible leading to cost reduction	Still under investigation as functional test
	Possible segmental functional evaluation	
Hepato-biliay scintigrphy (HBS)	Determine functional regional differences between liver segments	Specific competence needed
	Simultaneous hepatic uptake and bile secretion examination	Exposition to ionizing radiation (SPECT/CT)
	Validated even for parenchymal liver disease	
	Established and validated in literature even for two-stage procedures	

postoperative outcomes. Nuclear imaging studies and MRI present the unique ability to allow a precise evaluation of the segmental liver function, providing crucial information in the pre-operative work-out of two-stage procedures. For these reasons, a pre-operative combination between a dynamic quantitative test, such as ICG, with MRI or scintigraphy should enable a more complete functional evaluation, analyzing both the whole and residual liver. The choice between the several different available tests should be based on the patient's characteristics and center experience. Further trials are necessary to prospectively compare different functional tests to define the more accurate in predicting the risk of PHLF.

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