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ORIGINAL ARTICLE

Hepatobiliary scintigraphy to predict postoperative liver failure after major liver resection; a multicenter cohort study in 547 patients

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Abstract

Background: This study aimed to analyze the predictive value of Hepatobiliary scintigraphy (HBS) for posthepatectomy liver failure (PHLF) after major liver resection with a comparison to assessment of liver volume in a multicenter cohort.

Methods: Patients who underwent liver resection after HBS were included from six centers. Remnant liver volume was calculated from CT images. PHLF was scored and graded according to the grade B/C ISGLS criteria.

Results: In 547 patients PHLF incidence was 10% (56/547) and 90-day mortality rate 8% (42/547). Overall predictive value of remnant liver function was 0.66 (0.58−0.74) and similar to that of remnant volume (0.63 (0.72). For biliary tumors, a function cut-off of 2.7%/min/m2 and 30% volume cut-off resulted in a PHLF rate 12% and 13%, respectively. While an 8.5%/min (4.5%/min/m2) function cut-off resulted in 7% PHLF for those with a function above the cutoff while a 40% volume cutoff still resulted in 14% PHLF rate. In the multivariable analyses for PHLF, liver function was predictive but liver volume was not.

Conclusion: The current study shows that preoperative liver function assessment using HBS is at least as predictive for PHLF as liver volume assessment, and likely has several advantages, particularly in the high-risk sub-group of biliary tumors.

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Introduction

Posthepatectomy liver failure (PHLF) remains the single most important complication after major liver resection and is the main driver of postoperative mortality.[1] The incidence of PHLF varies between series due to the included patient groups and on the used definition of liver failure.[2,3] While liver failure rates after major liver resection for colorectal liver metastases are 1−12%,[4] the incidence surpasses 20% after resection for primary liver tumors including perihilar cholangiocarcinoma and hepatocellular carcinoma.[5,6] There is no uniform validated definition of PHLF and many definitions and classifications have been proposed.[7] The definition and grading system proposed by the International Study Group of Liver Surgery (ISGLS) is most widely used.[8,9] Regardless of the definition, there is no effective treatment available and the mortality associated with PHLF is high, which is why prevention of PHLF is key.[9,10]

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Preoperative assessment of the future liver remnant (FLR) can estimate the risk of PHLF after surgery. The FLR can be quantified through various methods, of which volume assessment remains the current standard.[11] Several commonly used adaptations of liver volume calculations have been suggested to improve the predictive value for PHLF.[12–14] But liver volume remains a surrogate for liver function. This may work quite well under the assumptions of homogenous distribution and normal total liver function. Quantitative liver function testing, for instance hepatobiliary scintigraphy (HBS) with technetium labeled mebrofenin has been suggested to improve the predictive value for remnant liver function.[15,16] The advantage of HBS over other functional tests such as indocyanine green (ICG) clearance and LIMAX (^{13}C-methacetin breath) metabolic tests is that it does not only measure total function but also shows its distribution. This is especially relevant in patients with deformed anatomy, after portal vein embolization or other augmentative procedures, underlying liver or biliary disease and after chemotherapy. Current evidence on HBS comes from single center series and does not definitively support widespread implementation of this technique.

This study aimed to analyze the predictive value of hepatobiliary scintigraphy for PHLF after major liver resection with a comparison to assessment of remnant liver volume in a multicenter design.

Methods

All patients who underwent major liver resection (defined as the resection of at least three Couinaud liver segments)[17] after assessment of liver function with mebrofenin-labeled HBS between 2000 and 2020 were included. Six experienced liver surgery centers included all consecutive cases. For Amsterdam UMC the indication for HBS was a planned right hepatectomy for any indication, any major resection for perihilar cholangiocarcinoma, or any major liver resection for any indication that was considered to have a high risk of PHLF. In Ghent and Bologna, HBS is performed before every major liver resection. In Birmingham, Lille and Antwerp, HBS is performed for every major liver resection that is considered to have a high risk of PHLF. The study protocol was reviewed by the medical ethics committee of the Amsterdam UMC and there was no need for ethical approval or individual informed consent according to Dutch law. All data was handled anonymously.

Hepatobiliary scintigraphy was performed according to the standard protocol developed at the Amsterdam UMC and applied with minor local adaptations in each center.[18] Only patients who underwent SPECT in order to quantify regional liver function were included. All preoperatively calculated liver functions were adjusted to be in accordance with the actually performed surgical resection. FLR function was expressed as %/min/m^2. All patients for whom no FLR volume calculation was available were excluded. Liver volume was measured on CT images and FLR volume was expressed as the percentage of total liver volume. Alternatively standardized FLR (sFLR) volume was calculated according to the formula of Vauthey et al.[13] Remnant liver to body weight ratio was calculated according to the method of Truant et al.[19] For patients who underwent preoperative portal vein embolization the liver function and volume measurements after embolization were used in the analyses.

Liver failure was defined and graded according to the International Study Group of Liver Surgery (ISGLS), and only grades B and C were considered to be of clinical relevance.[9] Biliary leakage and hemorrhage were also defined and graded according to the respective ISGLS criteria, and only grades B and C were included as clinically relevant. Ascites was defined as drainage of more than 200 cc/24 h after postoperative day 3 with an operative drain or abdominal distention with ascites seen on ultrasound. Grade B ascites was defined as the need for invasive treatment without general anesthesia or more than 1000 cc/24 h after postoperative day 3 in patients with an operative drain. Grade C was defined as ascites that required treatment under general anesthesia or treatment in the intensive care.

All categorical data were presented as numbers with percentages and differences were tested using chi-square of Fisher's exact tests where appropriate. All continuous data were presented as medians with inter-quartile-ranges (IQR) and differences were tested using Mann–Whitney tests. Predictive value of variables was tested using receiver operating characteristic analyses and area under the curve values were shown with 95% confidence intervals (95%CI). Multivariable analysis was performed using binary logistic regression with all variables with a P value below 0.100 at univariable analyses included. All statistical analyses were performed using SPSS (Version 26.0, IBM, Chicago, IL) and figures were generated using Graphpad Prism (Version 9, Graphpad Inc., La Jolla, CA).

Results

In the study period 581 patients underwent preoperative hepatobiliary scintigraphy before liver resection. For 37 patients preoperative liver volume was not available and were excluded. A total of 547 i patients were included in the analyses. Baseline characteristics are shown in Table 1. The reason for liver surgery were colorectal liver metastases in 174 patients (32%) and perihilar cholangiocarcinoma in 146 patients (27%). Right liver resection was performed in 335 patients (61%) of which 125 patients underwent extended right liver resection. Biliary reconstruction was performed in 200 patients (37%).

Postoperative outcomes are shown in Table 2. Liver failure grade B or C was diagnosed in 56 patients (10%) and 90-day mortality rate was 8% (42/547). Liver failure was associated with a 64% mortality rate, compared to 1% in patients who did not suffer liver failure (36/56 versus 7/488, $P < 0.001$).

In the overall cohort, the predictive value of FLR function, FLR volume, and sFLR volume for liver failure was similar (Fig. 1a). When using a 2.7%/min/m^2 FLR liver function cutoff, the liver

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Table 1 Baseline and operative characteristics

	All	Liver failure	No liver failure	P
	N = 547	N = 56	N = 491	
Age, *median (IQR)*	63 (54–71)	67 (57–73)	63 (54–70)	0.234
Male gender, *n (%)*	287 (53)	36 (64)	251 (51)	0.115
ASA classification, *III or IV, n (%)*	74 (15)	10 (18)	64 (13)	0.694
Diagnosis, *n (%)*				0.022
Colorectal liver metastases	174 (32)	15 (27)	159 (32)	
Perihilar cholangiocarcinoma	146 (27)	26 (46)	120 (24)	
Hepatocellular carcinoma	78 (14)	5 (9)	73 (15)	
intrahepatic cholangiocarcinoma	47 (9)	8 (14)	39 (8)	
Non colorectal liver metastases	16 (3)	–	16 (3)	
Hepatocellular adenoma	14 (3)	–	14 (3)	
Other diagnosis	72 (13)	2 (4)	70 (14)	
Previous abdominal surgery, *n (%)*	246 (45)	24 (43)	222 (45)	0.669
Previous liver surgery, *n (%)*	26 (5)	1 (2)	25 (5)	0.216
Baseline INR, *median (IQR)*	1.01 (0.99–1.10)	1.03 (0.99–1.14)	1.01 (0.99–1.09)	0.408
Baseline Bilirubin, *umol/L, median (IQR)*	9 (7–14)	11 (7–20)	9 (6–13)	0.206
Portal vein embolization, *n (%)*	118 (22)	9 (16)	109 (20)	0.291
Total liver volume, *mL, median (IQR)*	1661 (1407–2015)	1768 (1437–2082)	1646 (1405–1993)	0.237
FLR volume, *mL, median (IQR)*	706 (513–1042)	575 (426–760)	722 (524–1059)	0.006
FLR share, *%, median (IQR)*	41.6 (32.5–62.7)	35.0 (26.7–46.3)	42.2 (33.0–64.2)	0.009
Standardized FLR share, *%, median (IQR)*	45.9 (34.0–65.5)	35.4 (28.0–55.6)	46.8 (34.5–66.1)	0.113
Total liver function, *%/min, median (IQR)*	14.6 (12.5–16.6)	14.6 (10.4–17.0)	14.6 (12.7–16.5)	0.370
FLR functional share, *%, median (IQR)*	49.4 (36.0–71.0)	40.0 (27.0–65.0)	50.0 (37.0–71.2)	0.001
FLR function, *%/min/m2, median (IQR)*	3.9 (2.8–5.5)	3.0 (2.2–4.3)	4.0 (2.9–5.6)	0.001
Resection type, *n (%)*				<0.001
Left hepatectomy	147 (27)	8 (14)	139 (28)	
Extended left hepatectomy	25 (5)	9 (16)	16 (3)	
Right hepatectomy	228 (42)	21 (38)	207 (42)	
Extended right hepatectomy	125 (23)	17 (30)	108 (22)	
Segmentectomy	22 (4)	1 (2)	21 (4)	
Caudate resection, *n (%)*	162 (30)	29 (52)	133 (27)	<0.001
Hilar lymphadenectomy	232 (42)	35 (63)	197 (27)	0.005
Portal vein resection	45 (8)	5 (9)	40 (8)	0.799
Vena cava resection	13 (2)	1 (2)	12 (2)	0.756
Bile duct resection	200 (37)	34 (61)	166 (34)	<0.001

failure rate was 21% (24/112) in those below the cut-off, and 7% (32/435) in those above the cutoff ($P < 0.001$). When using 30% as a FLR volume cutoff, liver failure rate was 22% (21/97) in those below the cutoff, and 8% (35/450) in those above the cut-off ($P < 0.001$). The FLR volume and function for each individual patient in relation to liver failure is shown in Fig. 2a.

Abiding by the 2.7%/min/m2 FLR function and 30% FLR volume cut-off, 385 patients met both cutoffs (89%) with a 6% liver failure rate (24/385). Forty-seven (9%) did not meet both cutoffs with a 28% liver failure rate (13/47). FLR volume was sufficient, but function insufficient in 65 patients (12%), and 17% suffered liver failure (11/65). FLR volume was insufficient with sufficient function in the remaining 50 patients (9%) with a 16% liver failure rate (8/50). The predictive value of all volume and function parameters are shown in Table 3.

Risk factors for failure were identified using uni- and multivariable analyses, which are shown in Table 4. While FLR and FLR function were both associated with liver failure at univariable analyses, only FLR function was identified as risk factor for liver failure at multivariable analysis. For patients with biliary tumors this did not reach statistical significance at multivariable analysis (P = 0.058), however, the odds ratio was 2.20.

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Table 2 Postoperative outcomes

	All, N = 547	Liver failure, N = 56	No liver failure, N = 491	P
INR, *day 5, median (IQR)*	1.10 (1.00–1.32)	1.49 (1.22–2.01)	1.10 (1.00–1.26)	<0.001
Bilirubin, *day 5, umol/L, median (IQR)*	19 (12–34)	62 (30–116)	18 (12–31)	<0.001
Bilirubin, *peak, umol/L, median (IQR)*	29 (17–55)	139 (76–248)	27 (17–46)	<0.001
Liver failure, *ISGLS grade B/C. n (%)*	56 (10)	56 (100)	–	–
Ascites, *grade B/C, n (%)*	58 (11)	12 (21)	46 (9)	0.010
Biliary leakage, *ISGLS grade B/C, n (%)*	86 (16)	19 (34)	67 (14)	<0.001
Hemorrhage, *ISGLS grade B/C, n (%)*	28 (5)	14 (25)	14 (3)	<0.001
CCI, *median (IQR)*	20.9 (0.0–37.2)	100 (46.5–100.0)	20.9 (0.0–33.5)	<0.001
Readmission rate, *n (%)*	75 (14)	4 (7)	71 (14)	0.213
90-day mortality, *n (%)*	42 (8)	36 (64)	7 (1)	<0.001

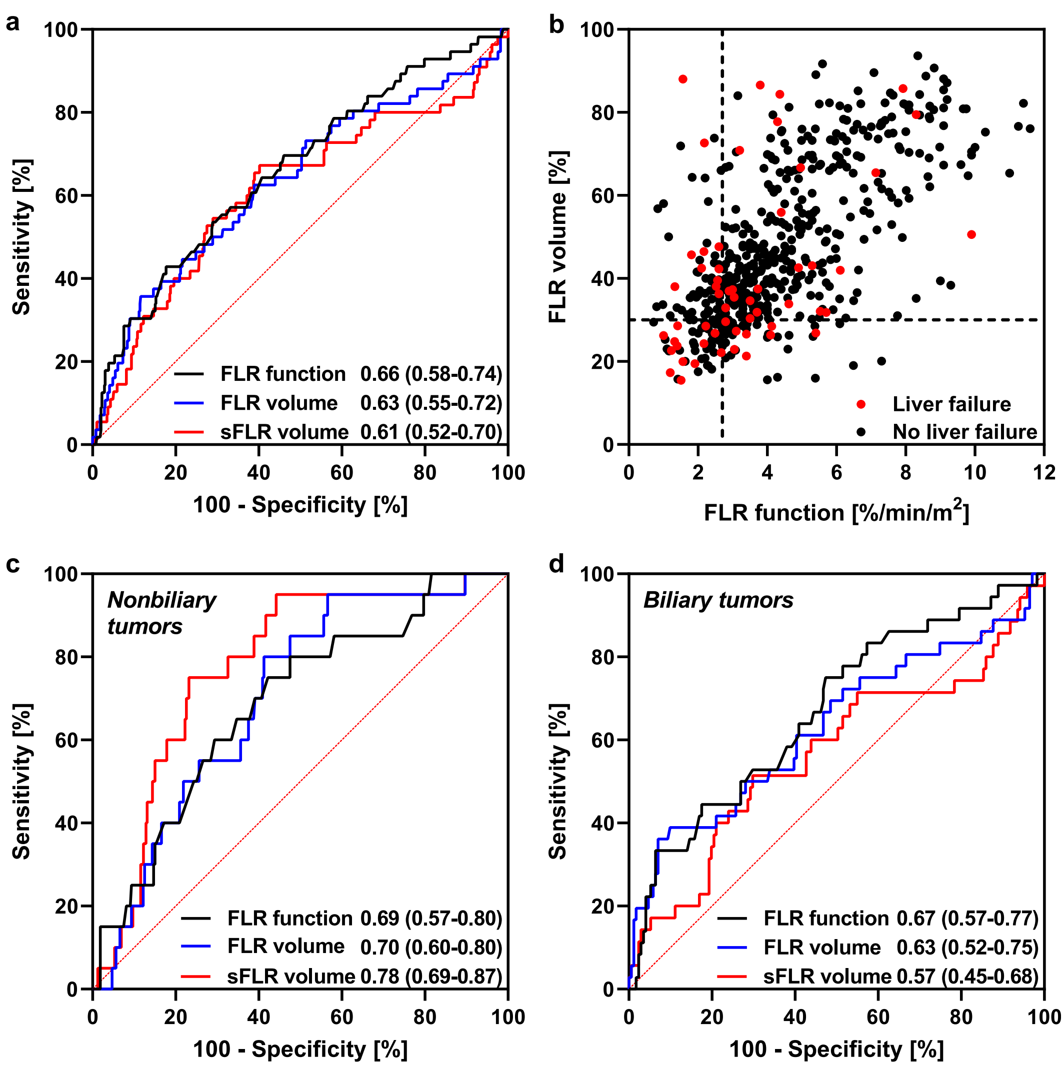

Figure 1 **(a)** ROC curve analysis for liver failure in the entire cohort. **(b)** Volume and function in each individual patient. **(c)** ROC curve analysis for liver failure for non-biliary tumors. **(d)** ROC curve analysis for liver failure in biliary tumors.

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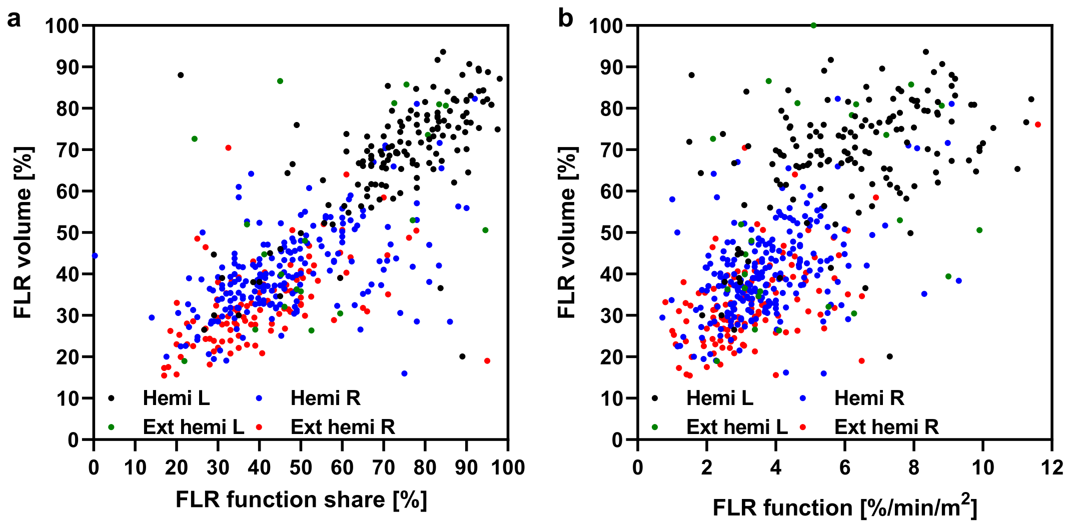

Figure 2 **(a)** Distribution of FLR volume and FLR function share across different types of liver resections. **(b)** Distribution of FLR volume and FLR function across different types of liver resections.

Table 3 Sensitivity, specificity, positive predictive value and negative predictive value of commonly used liver volume and function parameters

Cohort		Sensitivity	Specificity	PPV	NPV
Entire	2.7%/min/m^2	42.86	82.08	21.43	92.64
	30% FLR volume	37.50	84.52	21.65	92.22
	30% sFLR volume	30.91	85.51	19.32	91.68
	0.5% FLR/BW ratio	53.57	64.69	14.78	92.42
Non-biliary	2.7%/min/m^2	40.00	81.88	12.12	95.62
	30% FLR volume	35.00	85.00	12.73	95.44
	30% sFLR volume	55.00	82.13	16.18	96.68
	0.5% FLR/BW ratio	70.00	61.13	10.14	97.01
Biliary	2.7%/min/m^2	44.44	82.46	17.39	87.58
	8.5%/min	83.33	47.95	25.21	93.18
	30% FLR volume	38.89	83.63	33.33	86.67
	40% FLR volume	52.78	61.40	22.35	86.07
	0.5% FLR/BW ratio	44.44	71.35	24.62	85.92

Liver failure rate was high in the biliary tumor group with an incidence of 17% (36/207), compared to 6% patients with other diagnoses (20/340, $P < 0.001$). In the non-biliary tumor group the predictive value for liver failure was shown in Fig. 1c. In contrast to the entire cohort, the AUC value of sFLR volume was 0.78 (0.69–0.87), 0.70 (0.57–0.80) for FLR volume, and 0.69 (0.57–0.80) for FLR function. Using the 2.7%/min/m2 FLR function cut-off, liver failure rate was 12% for those below the cutoff (8/66) and 4% for those above the cut-off (12/274). Using the 30% FLR volume cut-off, liver failure rate was 13% for those below the cut-off (7/55) and 5% for those above it (13/285). Using a 30% sFLR volume cut-off, liver failure rate was 16% for those below the cut-off (11/68) and 3% for those above it (9/271). The predictive value of the parameters are summarized in Table 3.

The predictive value for patients with biliary tumors is shown in Fig. 1d, with values similar to that in the overall cohort. The 2.7%/min/m2 FLR function and 30% FLR volume cut-offs both resulted in a liver failure rate over 10% in patients meeting the cut-offs. For the 2.7%/min/m2 function cut-off, liver failure rate was 35% for those below it (16/46) and 12% for those above it (20/161). For the 30% volume cut-off, liver failure rate was 33% for those below it (14/42) and 13% for those above it (22/165). 23 patients were below both cut-offs and liver failure was 39% (9/23). Above both cut-off were 142 patients with 11% liver failure (15/142). Insufficient function and sufficient volume resulted in 30% liver failure (7/23) and sufficient function but insufficient volume in 26% liver failure (5/19).

A 40% FLR volume cut-off results in 22% liver failure for those below it (19/85) and 14% for those above it (17/122). A previously proposed 8.5%/min (unknot corrected for bodysurface area (BSA)) FLR function cut-off results in a 25% liver failure rate for those below it (30/119) and 7% for those above it (6/88). The 8.5%/min cut-off approximates 4.5%/min/m2 when the 8.5 is divided by the median BSA value. For patients with a biliary tumor, FLR volume above 40% and FLR function above 8.5%/min, liver failure rate was 6% (5/82). Those with FLR volume below 40% and function below 8.5%/min, liver failure rate was 23% (18/79). For patients with volume below 40%, but function above 8.5%/min, liver failure occurred in 17% (1/6). For patients with volume above 40%, but function below 8.5%/min, liver failure rate was 30% (12/40). The predictive value of the volume and function parameters are summarized in Table 4.

The distribution of FLR liver volume in relation to FLR function share (in %) was shown in Fig. 1b. The discrepancies between these parameters was low for left hemihepatectomies while the

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Table 4 Uni- and multivariable analysis for liver failure

	Univariable analysis		Multivariable analysis	
	Odd ratio (95%CI)	P	Odd ratio (95%CI)	P
Age, *continuous*	1.02 (0.99–1.04)	0.140		
Male sex	1.64 (0.91–2.96)	0.101		
ASA, *III/IV versus I/II*	1.22 (0.61–2.43)	0.578		
Biliary tumor	3.37 (1.89–6.00)	<0.001	2.20 (0.98–4.96)	0.058
Right liver resection	1.18 (0.65–2.13)	0.584		
Extended liver resection	2.57 (1.46–4.51)	0.001	1.05 (0.51–2.17)	0.902
Caudate resection	2.60 (1.45–4.67)	0.001	1.80 (0.86–3.78)	0.121
Bile duct resection	3.01 (1.71–5.31)	<0.001	1.59 (0.71–3.56)	0.256
Portal vein resection	1.07 (0.41–2.84)	0.887		
FLR volume share, *%, continuous*	0.98 (0.96–0.99)	0.007	0.99 (0.97–1.01)	0.341
FLR function, *%/min/m2, continuous*	0.74 (0.62–0.88)	0.001	0.76 (0.62–0.94)	0.012

mismatch was greater for (extended) right hemihepatectomy. This difference was less pronounced when comparing FLR volume to absolute FLR function (in %/min/m^2) (Fig. 2b).

Discussion

This series is the largest to date to report on HBS compared to volume to predict PHLF. A total of 547 patients who underwent major liver resection after assessment of both liver volume and function were included in the analysis. The most important finding is that, in the multivariable analyses for PHLF, liver function was predictive of PHLF but liver volume was not. In patients with biliary tumors the previously proposed 2.7%/min/m2 liver function and 30% liver volume cutoffs for the FLR resulted in a PHLF rate 12% and 13%, respectively. While a 8.5%/min (4.5%/min/m2) function cut-off resulted in 7% PHLF for those with a function above the cutoff, a 40% volume cutoff still resulted in 14% PHLF rate.

The additional value of mebrofenin-labeled hepatobiliary scintigraphy in the prediction of PHLF was shown in a prospective trial in 2010.[15] In this trial of 55 patients, the FLR function of 2.7%/min/m^2 resulted in a positive predictive value of 57% and negative predictive value of 98%. These excellent predictive values should be interpreted in comparison to liver volume, a 30% volume cut-off for normal and 40% for compromised livers resulted in a positive predictive value of 44% and a negative predictive value of 95%. Therefore the additional predictive value of HBS was limited and the implementation in clinical practice has been slow. Nevertheless, subsequent studies have illustrated a reduction of PHLF and mortality following implementation of HBS.[20] In particular for very-high risk surgery, such as for perihilar cholangiocarcinoma.[5]

The liver function value of 2.7%/min/m^2 has not been truly validated to date. Since its introduction in 2010, this value has been the standard for liver function at the Amsterdam UMC and consequently there are very few patients undergoing surgery with a liver function value below 2.7%/min/m^2 and therefore no statistical power to allow any further validation. Recently, several centers have implemented HBS in their preoperative work up and found similar results. A study on 38 patients reported that a FLR function of at least 1.9%/min/m^2 could prevent PHLF grade B/C and a FLR function of 2.8% could prevent any grade PHLF.[21] Another larger study on 88 patients found a function of 2.3%/min/m^2 effectively predicted PHLF with a positive predictive value of 92% and a negative predictive value of 97%.[22] Although these were not formal prospective validation studies, the similar results underscore the validity of the proposed liver function cut-off. The range from 1.9 to 2.8 indicates that it is probably too simplistic to use an absolute dichromate "cut-off value" as PHLF is often multifactorial.

The predictive value of liver volume might especially be insufficient in high-risk patients with compromised liver parenchyma. For instance, prolonged preoperative chemotherapy of more than 6 cycles is known to be associated with chemotherapy associated liver injury. This injury in turn increases morbidity and the risk of PHLF after major liver resection.[23,24] Liver volume assessment alone does not provide insight in the chemotherapy induces liver injury, but a recent study showed that HBS can detect patients with compromised liver function secondary to chemotherapy associated liver-injury.[25] Therefore HBS might be indicated in patients scheduled for major liver resection after extensive chemotherapy. Screening for underlying liver disease of damage using HBS might be able to prevent unnecessary liver biopsies.

Other high risk patients includes those with biliary tumors, who often suffer from obstructive cholestasis which is known to impair liver function. Although biliary drainage is common, major liver resection in patients with biliary tumors is still associated with high rates of PHLF and mortality.[26–28] A recent study showed that the variation in anatomical liver volume and functional distribution is especially divergent in patients with primary tumors.[29] A previous study reported on the additional

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predictive value of HBS for patients with perihilar cholangiocarcinoma. The current data showed liver volume measures and the general 2.7%/min/m^2 are not sufficient to prevent PHLF. This study confirmed that in order to perform a safe major liver resection, a higher FLR function of 8.5%/min (4.5%/min/m2) should be present. The importance of this finding is illustrated by the high PHLF and mortality rates in patients with biliary tumors that exceed the rates seen in other patient groups.

The final high-risk liver resection group that illustrates the additional predictive value of HBS is that of two-stage resections, in particular associating liver partition with portal vein ligation for staged hepatectomy (ALPPS). The initial introduction of ALPPS came with high mortality and PHLF rates, which might be attributable to the lack in functional increase in spite of the rapid volume growth associated with ALPPS.[30] Two multicenter studies have shown the additional predictive value of HBS in the context of ALPPS over liver volume alone.[30,31] Considering the mismatch in liver volume and function increase in ALPPS, HBS might be of upmost important when planning the second stage of ALPPS. The mismatch in liver volume and function was also evident in formal hepatectomies in this study, especially in resections other than left liver resections when comparing FLR volume to FLR function share. However, since FLR function share is a relative value and dependent on total liver function, the mismatch in volume and function is evident in all resection type subgroups when comparing FLR volume to FLR function. These findings again highlight the relevance of functional testing in patients at risk of PHLF.[29]

Aside from the added predictive value of HBS in high-risk resections, the multivariable analysis for liver failure illustrates the relevance of functional assessment. While liver volume was not a predictor for PHLF, liver function was. Corrected for relevant variables, the use of liver function is therefore likely able to identify patients at high-risk of liver failure in the absence of other relevant predictors of PHLF.

This study has several limitations, mostly related to the retrospective study design and unavoidable selection bias, for instance, patients who were not operated but did undergo liver function assessment were not included in this study. Several studies have already shown the high risk of liver failure associated with low liver function measurements, therefore the number of patients with low liver function in this study is low. This is likely the main reason why the predictive value of HBS seen in the first study from 2010 was not reached. The limited number of PHLF in the non-biliary group (20/340) compared to the biliary (36/207) may not be sufficient to demonstrate a clear additional value of function in the non-biliary group. Complications subject patients to an increased risk of liver failure. There was insufficient data on the timing of complications to include this in the analysis. This is the first multicenter series on HBS before major liver resection, however, the evidence presented does not completely justify its implementation in every center that performs liver surgery. A prospective trial, preferably randomized trial is needed to demonstrate with high level of certainty that HBS should be the gold standard, but comes with several practical challenges. A randomized prospective trial would rquire thousands of included patients which is clearly not feasible. Centers that routinely use HBS will probably be very reluctant to participate in such a trial due to their positive experiences with HBS and may believe it to be unethical to perform only volume assessment of the FLR. Perhaps a large series such as the current study is the highest level of evidence we can practically achieve.

The current study shows that preoperative liver function assessment using HBS is at least as predictive for PHLF as liver volume assessment, and likely has several advantages. The absence of liver volume as predictor in the multivariable analysis when liver function is included suggests HBS can aid to identify patients at unexpected high risk of liver failure, or at least improve the predictive value when using both liver function and liver volume assessment In patients with biliary tumor that are at high risk of liver failure, liver function assessment more effectively stratified patients according to the risk of PHLF. While the 2.7%/min/m^2 seems appropriate for most patients, the risk of PHLF in patients with biliary tumors can potentially be reduced when a liver function cut-off of 8.5%/min (4.5%/min/m2) is used. For these patients with biliary tumors, liver volume is of value in the preoperative work up, but liver function assessment might be able to help to improve the outcomes.

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Conflict of interest

None to declare.

References

1. van Mierlo KM, Schaap FG, Dejong CH, Olde Damink SW. (2016) Liver resection for cancer: new developments in prediction, prevention and management of postresectional liver failure. *J Hepatol* 65: 1217–1231.
2. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. (2012) How much remnant is enough in liver resection? *Dig Surg* 29:6–17.
3. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al*. (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 236:397–406. ; discussion -7.
4. Narita M, Oussoultzoglou E, Bachellier P, Jaeck D, Uemoto S. (2015) Post-hepatectomy liver failure in patients with colorectal liver metastases. *Surg Today* 45:1218–1226.
5. Olthof PB, Coelen RJS, Bennink RJ, Heger M, Lam MF, Besselink MG *et al*. (2017) (99m)Tc-mebrofenin hepatobiliary scintigraphy predicts liver failure following major liver resection for perihilar cholangiocarcinoma. *HPB* 19:850–858.

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6. Hemming AW, Gallinger S, Greig PD, Cattral MS, Langer B, Taylor BR *et al*. (2001) The hippurate ratio as an indicator of functional hepatic reserve for resection of hepatocellular carcinoma in cirrhotic patients. *J Gastrointest Surg* 5:316–321.
7. van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malago M, Jalan R *et al*. (2008) Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int* 28: 767–780.
8. Sultana A, Brooke-Smith M, Ullah S, Figueras J, Rees M, Vauthey JN *et al*. (2018) Prospective evaluation of the International Study Group for Liver Surgery definition of post hepatectomy liver failure after liver resection: an international multicentre study. *HPB* 20:462–469.
9. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R *et al*. (2011) Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). *Surgery* 149:713–724.
10. Skrzypczyk C, Truant S, Duhamel A, Langlois C, Boleslawski E, Koriche D *et al*. (2014) Relevance of the ISGLS definition of post-hepatectomy liver failure in early prediction of poor outcome after liver resection: study on 680 hepatectomies. *Ann Surg* 260:865–870. ; discussion 70.
11. Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K *et al*. (1997) Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 26:1176–1181.
12. Truant S, Oberlin O, Sergent G, Lebuffe G, Gambiez L, Ernst O *et al*. (2007) Remnant liver volume to body weight ratio > or =0.5%: a new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. *J Am Coll Surg* 204:22–33.
13. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C *et al*. (2000) Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 127:512–519.
14. Olthof PB, van Dam R, Jovine E, Campos RR, de Santibanes E, Oldhafer K *et al*. (2019) Accuracy of estimated total liver volume formulas before liver resection. *Surgery* 166:247–253.
15. de Graaf W, van Lienden KP, Dinant S, Roelofs JJ, Busch OR, Gouma DJ *et al*. (2010) Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. *J Gastrointest Surg* 14:369–378.
16. Rassam F, Olthof PB, Bennink RJ, van Gulik TM. (2017) Current modalities for the assessment of future remnant liver function. *Vis Media* 33:442–448.
17. Bismuth H. (2013) Revisiting liver anatomy and terminology of hepatectomies. *Ann Surg* 257:383–386.
18. Rassam F, Olthof PB, Richardson H, van Gulik TM, Bennink RJ. (2019) Practical guidelines for the use of technetium-99m mebrofenin hepatobiliary scintigraphy in the quantitative assessment of liver function. *Nucl Med Commun* 40:297–307.
19. Truant S, Boleslawski E, Sergent G, Leteurtre E, Duhamel A, Hebbar M *et al*. (2015) Liver function following extended hepatectomy can be accurately predicted using remnant liver volume to body weight ratio. *World J Surg* 39:1193–1201.
20. Cieslak KP, Bennink RJ, de Graaf W, van Lienden KP, Besselink MG, Busch OR *et al*. (2016) Measurement of liver function using hepatobiliary scintigraphy improves risk assessment in patients undergoing major liver resection. *HPB* 18:773–780.
21. Serenari M, Bonatti C, Zanoni L, Peta G, Tabacchi E, Cucchetti A *et al*. (2021) The role of hepatobiliary scintigraphy combined with spect/ct in predicting severity of liver failure before major hepatectomy: a single-center pilot study. *Updates Surg* 73:197–208.
22. Chapelle T, Op De Beeck B, Huyghe I, Francque S, Driessen A, Roeyen G *et al*. (2016) Future remnant liver function estimated by combining liver volumetry on magnetic resonance imaging with total liver function on (99m)Tc-mebrofenin hepatobiliary scintigraphy: can this tool predict post-hepatectomy liver failure? *HPB* 18:494–503.
23. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D *et al*. (2010) Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. *Ann Surg Oncol* 17: 2870–2876.
24. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B *et al*. (2006) Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 243:1–7.
25. Truant S, Baillet C, Gnemmi V, Fulbert M, Turpin A, Dardenne S *et al*. (2021) The impact of modern chemotherapy and chemotherapy-associated liver injuries (CALI) on liver function: value of 99mTc-labelled-mebrofenin SPECT-hepatobiliary scintigraphy. *Ann Surg Oncol* 28:1959–1969.
26. Mazzaferro V, Gorgen A, Roayaie S, Droz Dit Busset M, Sapisochin G. (2020) Liver resection and transplantation for intrahepatic cholangiocarcinoma. *J Hepatol* 72:364–377.
27. Franken LC, Schreuder AM, Roos E, van Dieren S, Busch OR, Besselink MG *et al*. (2019) Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: a systematic review and meta-analysis. *Surgery* 165:918–928.
28. Olthof PB, Wiggers JK, Groot Koerkamp B, Coelen RJ, Allen PJ, Besselink MG *et al*. (2017) Postoperative liver failure risk score: identifying patients with resectable perihilar cholangiocarcinoma who can benefit from portal vein embolization. *J Am Coll Surg* 225:387–394.
29. Dasari BVM, Wilson M, Pufal K, Kadam P, Hodson J, Roberts KJ *et al*. (2021) Variations between the anatomical and functional distribution, based on 99(m) technetium -mebrofinate SPECT-CT scan. In: *Patients at risk of post hepatectomy liver failure*. Oxford): HPB.
30. Olthof PB, Tomassini F, Huespe PE, Truant S, Pruvot FR, Troisi RI *et al*. (2017) Hepatobiliary scintigraphy to evaluate liver function in associating liver partition and portal vein ligation for staged hepatectomy: liver volume overestimates liver function. *Surgery* 162:775–783.
31. Tomassini F, D'Asseler Y, Linecker M, Giglio MC, Castro-Benitez C, Truant S *et al*. (2020) Hepatobiliary scintigraphy and kinetic growth rate predict liver failure after ALPPS: a multi-institutional study. *HPB* 22: 1420–1428.

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