Received: 7 June 2023 | Accepted: 12 August 2023

DOI: 10.1002/jso.27426

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Tc-99m mebrofenin hepatobiliary scintigraphy to assess future liver remnant function before major liver surgery

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Abstract

Background and Objectives: Assessment of liver function is paramount before hepatectomy. This study aimed to assess future liver remnant function (FLR-F) using hepatobiliary scintigraphy (HBS) and to compare it to FLR volume (FLR-V) in the prediction of posthepatectomy liver failure (PHLF). The impact of volume and function gains were also assessed in patients undergoing portal vein embolization (PVE) or liver venous deprivation (LVD).

Methods: All consecutive patients undergoing major hepatectomy between 02/2018 and 09/2021 with preoperative HBS were included. FLR-V was expressed as percentage of total liver volume and analyzed using preoperative computed tomography. FLR-V and FLR-F gains after embolization were expressed in percentage. Receiver operating characteristic analysis was performed to compare both methods in predicting PHLF.

Results: Thirty-six patients were included. PVE and LVD were performed in 4 (11%) and 28 patients (78%), respectively. Overall, PHLF occurred in eight patients (22%). FLR-F gain after embolization showed significant ability to predict PHLF (area under the curve [AUC] = 0.789), with cut-off value of 150% showing a sensitivity of 1.00, a specificity of 0.42, and a negative predictive value of 1.00.

Conclusion: Preoperative HBS shows a high sensitivity to predict PHLF when HBS is performed twice to measure the function gain after venous embolization.

KEYWORDS

hepatectomy, hepatobiliary scintigraphy, liver failure, liver function test

Héloïse Smet and David Martin are shared first authorship.

1 | INTRODUCTION

Major hepatectomy is the only curative option for a multitude of hepatobiliary cancers. According to the extent of resection, liver failure is the most life-threatening complication that can occur, with an incidence range between 0.7% and 9.1%.[1] Posthepatectomy liver failure (PHLF) accounts for nearly half of in-hospital mortality.[1,2]

Several risk factors are associated with PHLF including patient factors, underlying disease, intra- and postoperative events.[3] One of the most important risk factors in the occurrence of PHLF is the quality of the liver parenchyma. Consequently, the evaluation of liver function and volume is paramount in the preparation of a major hepatectomy; especially since it is one of the potentially modulating factors.

CT-based volumetry remains the primary tool to evaluate future liver remnant volume (FLR-V), expressed in percentage of total liver volume (TLV). The thresholds of FLR-V of 25–30% in patients with normal liver and of 40% in diseased liver (cirrhosis or after chemotherapy) have been suggested.[4,5] One of the main limitations is that the estimated volume does not necessarily correlate with liver function. Hepatobiliary scintigraphy (HBS) allows the evaluation of liver function and is increasingly used worldwide in the preoperative work-up before major liver resection. It allows a functional evaluation of the liver by measuring hepatocytes uptake of mebrofenin coupled with Technetium-99m (^{99m}Tc). HBS combined with single-photon emission computed tomography coupled with CT-scanner (SPECT/CT) is a quantitative method leading to the evaluation of total and regional liver function allowing an assessment of the future remnant liver function (FLR-F).[6]

Portal vein embolization (PVE) induces a hypertrophy and consequently a function increase of the FLR.[7] More recently, liver venous deprivation (LVD) has been developed and consists in the simultaneous embolization of ipsilateral portal and hepatic veins. It seems that LVD is associated to better results regarding FLR kinetic of growth and function compared to PVE alone.[8,9] A remnant liver function cut-off value of 2.7%/min/m^2 has been recommended by De Graaf et al. to predict the risk of PHLF.[6] Currently, only few data are available to confirm the sensitivity of HBS to assess the risk of PHLF. Beyond the functional evaluation of the FLR at a certain timepoint, function and volume gain assessment in the context of a portal embolization may provide some additional information to estimate the risk of PHLF.

This study aimed to assess FLR-F using ^{99m}Tc-mebrofenin HBS before major liver surgery and to compare it to FLR-V in the prediction of PHLF. In addition, the impact of volume and function gains were assessed in patients who underwent PVE or LVD.

2 | METHODS

2.1 | Study design and patients

This single-center retrospective study included all consecutive patients undergoing major liver resection at the Department of Visceral Surgery, University Hospital CHUV, Lausanne, Switzerland, between February 2018 and September 2021, and who had preoperative ^{99m}Tc-mebrofenin HBS to assess FLR-F. Patients with disease progression after embolization were excluded. This study was approved by the Local ethics committee (ID# 2021-00610).

All treatment decisions were discussed and validated in a dedicated tumor board meeting (MDT), and major liver resections were defined as the removal of ≥3 liver segments. All patients were managed according to the Enhanced Recovery After Surgery protocol.[10] When the preoperative liver volume was deemed insufficient, PVE with or without hepatic vein embolization was performed to increase the size of the future liver remnant, according to a decision algorithm.[11]

Demographics, pathology, and intraoperative characteristics were collected. Postoperative outcomes included 30-day morbidity, 90-day mortality, and the length of hospital stay. Complications were graded according to the Clavien classification.[12] Major complications were defined as grades ≥ IIIa. The Comprehensive Complication Index (CCI) was calculated considering all complications with a score ranging from 0 to 100.[13] Postoperative liver failure and bile leakage were defined according to the International Study Group for Liver Surgery (ISLGS).[14,15] Grades B and C of liver failure were deemed as clinically relevant.

2.2 | Volumetric assessment

TLV as well as the FLR-V were calculated on CT acquisitions of the portal phase using a validated software (Synapse Vincent; Fujifilm®).[16] The ratio between FLR-V and the TLV was defined as the FLR ratio and expressed in percentage (%). FLR volume gain was defined as ([Postembolization FLR-V]/[Postembolization TLV]) · 100/([Pre-embolization FLR-V]/[Pre-embolization TLV]) (%).[17] The kinetic growth rate (KGR) was calculated by the following formula: KGR = ([Postembolization FLR-V—Pre-embolization FLR-V]/[Pre-embolization FLR-V] ·100)/time elapsed since embolization (weeks) at first volume assessment (%/week).[18] All volumes were assessed by a trainee surgeon.

2.3 | Functional assessment

HBS was performed using ^{99m}Tc-mebrofenin as previously described.[6,19,20] FLR uptake function (FLR-F) was calculated by dividing counts within the delineated FLR by the total liver counts and multiplying this factor with total liver uptake (TL-F) and expressed as percent per minute per square meter of body surface area (%/min/m^2).[6] FLR function gain was defined as ([Postembolization FLRF]/[Postembolization TLF])·100/([Pre-embolization FLRF]/[Pre-embolization TLF]) (%). The KGR was calculated by the following formula: KGR = ([Postembolization FLR-F—Pre-embolization FLR-F]/[Pre-embolization FLR-F]·100)/time elapsed since embolization (weeks) at first function assessment (%/week). All HBS were assessed by a senior physician from the department of nuclear medicine.

2.4 | Statistical analysis

Continuous variables were expressed as mean (standard deviation, SD) or median (interquartile range, IQR) and compared with Mann–Whitney *U* test or Student's *t* test according to their distribution (Shapiro–Wilk test). Categorical variables were expressed as the frequency and percentage and compared between groups with Pearson's χ^2 or Fisher's exact test, where appropriate. Correlations between continuous variables were assessed with Pearson correlation coefficients. Pearson correlation coefficient were interpreted as follows: 0.00–0.09 negligible; 0.10–0.39 weak; 0.40–0.69 moderate; and 0.70–0.89 strong correlation.[21] Receiver operating characteristic (ROC) curve analysis was performed to evaluate both methods (volume and function) in predicting PHLF. A fair diagnostic performance was defined as a ROC curve having an area under the curve of at least 0.7. All analyses were performed with SPSS 26.0 (SPSS Inc.).

3 | RESULTS

A total of 44 consecutive patients were evaluated for a major hepatectomy, and 36 were included in the study. Four patients have not given their consent for research, three were diagnosed with extrahepatic progression before surgery, and one patient was diagnosed with peritoneal carcinomatosis at the time of surgery and did not benefit from surgical resection.

3.1 | Demographics, surgery, and outcomes

Patient's characteristics, surgical details and postoperative clinical outcomes are summarized in Table 1. Fifty-eight percent of the patients were male, and mean age was 61 years. Seventeen patients (47%) were operated for colorectal liver metastasis. Sixteen (44%) patients had a right hepatectomy and 15 (42%) had an extended right hepatectomy.

Twenty-nine (81%) patients developed a complication and mean ± SD CCI was 28.6 ± 24.0. Major complications occurred in 11 patients (31%) (Clavien-Dindo ≥ 3a), one of which was due to PHLF. This patient presented an acute liver failure due to hepatic vein twist of the remnant liver, which was successfully managed with an emergency reoperation.

Eight patients developed PHLF (22%) according to the ISGLS definition.[14] Four were classified grade B and one grade C. There was no postoperative mortality. There was significantly longer hospital stay ($p < 0.001$) and increased CCI ($p = 0.005$) in the PHLF group.

3.2 | Preoperative volumes and functions data

Overall, median FLR-V was 548 ml, which represent 37.5% of TLV. Median FRL-F was 1.9%/min/m^2. Twenty-three of the 36 studied patients (63.9%) were evaluated with a preoperative HBS and 32 of them (88.9%) had a preoperative volumetry.

Thirty-two patients (89%) needed a preoperative embolization due to insufficient FLR-V or FLR-F according to the preoperative work-up. Regarding non embolized patients, median FRL-F was 3.1%/min/m^2 (2.8–3.9), corresponding to 62% of TLF. Median FLR-V was 739.6 mL (637–843), which corresponds to 49.5% of TLV. In those who were embolized, 88% ($n = 28$) of them had LVD and 12% ($n = 4$) underwent PVE alone. Median FRL-F_1 before embolization was 1.9%/min/m^2 (1.4–2.3), corresponding to 33% of TLF; while median FRL-V_1 was 548 ml (475–835), corresponding to 36.5% of TLV. After embolization, median FRL-F_2 was 3.4%/min/m^2 (2.7–4.2), which corresponds to 53% of TLF_2. Median FLR-V_2 was 752 ml (650–953), which corresponds to 42.8% of TLV_2. Median function gain after venous embolization was 149% and median KGR-F was 8%/week, while median FLR volume gain was 113% and median KGR-V was 2.1%/week. (Figure 1). In total, 31 of the 32 embolized patients (96.9%) had a postembolization scintigraphy in a median time of 21 days (18.5–27.5) after embolization. All the embolized patients had a postembolization volumetry in a median time of 22 days (19–28). Overall, surgery was performed at a median time of 32 days (25–35) after embolization.

There was no correlation between future remnant liver function and volume ($r = 0.084$, $p = 0.625$) (Figure 2).

ROC curve analysis of FRL-F and FRL-V did not predict the occurrence of overall PHLF (area under the curve [AUC] = 0.378; 95% confidence interval [CI] 0.201–0.476 for FRL-V and AUC = 0.576; 95% CI: 0.247–0.690 for FRL-F; Figure 3A) and clinically relevant PHLF (AUC = 0.352; 95% CI: 0.117–0.566 for FRL-V and AUC = 0.665; 95% CI: 0.302–0.815 for FRL-F; Figure 3B). ROC curve analysis regarding FRL-V gain and KGR-V did not show an ability for PHLF prediction (AUC = 0.625, 95% CI: 0.351–0.899 for FLR volume gain and AUC = 0.566, 95% CI: 0.299–0.833 for KGR-V; Figure 4B). FRL-F gain and KGR-F showed a prognostic value to predict PHLF (respectively AUC = 0.789 (95% CI: 0.562–1.000) and AUC = 0.719 (95% CI: 0.518–0.921)). FLR-F gain after liver embolization showed significant ability to predict PHLF (AUC = 0.789), with cut-off value of 150% showing a sensitivity of 1.00, a specificity of 0.42, and a negative predictive value of 1.0.

4 | DISCUSSION

This study showed that FLR function gain and function kinetic growth rate using HBS after venous embolization are good predictors of liver insufficiency after major hepatectomy. On the other hand, one HBS absolute value for preoperative FRL function assessment in liver without venous manipulation did not predict PHLF. In addition, FLR volume gain, volume kinetic of growth, and FLR volume did not show an ability to predict postoperative liver failure, confirming that volume does not correlate with FLR function.

HBS with mebrofenin allows a functional evaluation of liver parenchyma and is increasingly used in the preoperative work-up

TABLE 1 Patient demographics.

	N = 36	No PHLF *N* = 31 (86%)	PHLF (B/C) *N* = 5 (14%)	*p* Value
Age (years) (mean, SD)	61 (±13)	60 (±13)	64 (±14)	0.463
Sex (male), (*n*, %)	21 (58)	20 (65)	1 (20)	0.138
BMI (kg/m^2) (mean, SD)	26.3 (±4.9)	26.3 (±4.7)	27 (±6.8)	0.964
ASA score grade ≥ 3, (*n*, %)	15 (42)	13 (41)	2 (40)	1.000
Cardiovascular disease, (*n*, %)	5 (14)	5 (14)	0 (0)	1.000
Diabetes, (*n*, %)	4 (11)	2 (7)	2 (40)	0.084
Indication for surgery, (*n*, %)				0.049
Hepatocarcinoma	5 (14)	5 (16)	0 (0)	
Hilar Cholangiocarcinoma	3 (8)	1 (3)	2 (40)	
Intra-hepatic cholangiocarcinoma	5 (14)	4 (13)	1 (20)	
Colo-rectal liver metastasis	17 (47)	16 (52)	1 (20)	
Benign lesion	4 (11)	3 (10)	1 (20)	
Neoadjuvant chemotherapy (*n*, %)	17 (47)	16 (52)	1 (20)	0.342
Preoperative biliary drainage (*n*, %)	6 (17)	4 (13)	2 (40)	0.186
Preoperative venous embolization (*n*, %)	32 (89)	28 (90)	4 (80)	0.466
Type of surgery				0.861
Right hepatectomy (*n*, %)	16 (44)	14 (45)	2 (40)	
Extended right hepatectomy (*n*, %)	15 (42)	12 (39)	3 (60)	
Left hepatectomy (*n*, %)	2 (6)	2 (7)	0 (0)	
Extended left hepatectomy (*n*, %)	3 (8)	3 (10)	0 (0)	
Intraoperative characteristics				
Operating time (min) (mean, SD)	362 (±122)	351 (±113)	432 (±167)	0.200
Blood loss (mL) (mean, SD)	1071 (±559)	1021 (±493)	1360 (±868)	0.054
Total ischemic time (min) (mean, SD)	13.6 (±15.6)	12.8 (±15.8)	19 (±15.1)	0.366
Background liver status				
Normal/fibrosis/steatosis/SOS	12/1/4/4	10/1/3/4	2/0/1/0	
Hospital length (day) (median, IQR)	13 (8–21)	14 (±9)	46 (±38)	<0.001
Complications (*n*, %)	29 (81)	24 (77)	5 (100)	
Major complication (*n*, %)	11 (31)	12 (39)	4 (80)	0.023
CCI (mean, SD)	28.6 (±24.0)	23.2 (±19.9)	61.3 (±21)	0.005
Hospital deaths (*n*, %)	0 (0)	0 (0)	0 (0)	

Abbreviations: ASA score, American Society of Anesthesiologists score; BMI, body mass index; CCI, Comprehensive complication index; PHLF, posthepatectomy liver failure; SOS, sinusoidal obstruction syndrome.

before major hepatectomy. Historically, De Graaf et al. have established a cut-off value of 2.7%/min/m^2[26] and HBS became, where available, a validated tool for preoperative liver function assessment.[22–24] However, data regarding the preoperative assessment of lobar liver function and the postoperative risk of liver failure are scarce. HBS results may be affected by cholestasis or hyperbilirubinemia.[25–27] Three types of receptors have been detected and seems to be associated with ^{99m}Tc-mebrofenin liver uptake kinetic. These include sinusoidal influx transporters (organic anion-transporting polypeptide) responsible for hepatic uptake of

^{99m}Tc-mebrofenin, and efflux transporters (Multidrug Resistance-associated Proteins [MRP]) mediating its canalicular and sinusoidal excretion.[27] In case of cholestasis, impaired biliary excretion results in increased blood exposure to ^{99m}Tc-mebrofenin because of extensive hepatic accumulation and increased sinusoidal efflux, suggesting the involvement of MRP3.[27] In the present study, 6 patients needed preoperative biliary drainage because of cholestasis. Median FRL-F_1 was 1.9 kg/min/m^2 and FRL-F_2 after venous embolization was 3.7 kg/min/m^2. None of the drained patients had cholestasis at the time of surgery and we did not observe a significant difference regarding the occurrence of PHLF in those patients (Table 1).

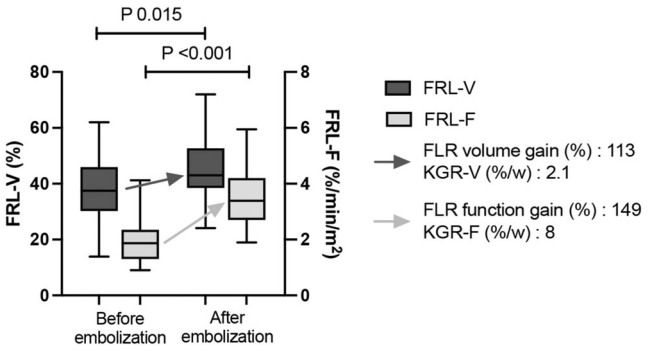

FIGURE 1 Comparison of FRL-V (%) and FRL-F (%/min/m^2) before and after embolization, with volume and function gains and KGR data. FRL-V. FRL-F. FLR volume gain (%): 113. KGR-V (%/week): 2.1. FLR function gain (%): 149. KGR-F (%/week): 8. FRL-F, future remnant liver function; FRL-V, future remnant liver volume; KGR, kinetic growth rate; KGR-F, kinetic growth rate function; KGR-V, kinetic growth rate volume.

In the present study, 8 patients (22%) experienced a post-operative liver insufficiency, while 5 (14%) were clinically relevant. These results may seem high but they should be taken into account that only major liver resection were analyzed. These data are comparable to those reported in other studies regarding major hepatectomies.[28,29] Several risk factors have been identified for postresectional liver failure.[1] In the present study, regarding operative factors, only blood loss was more important in the PHLF-group, without being significantly different. Concerning patient related data, both groups were equivalent except regarding diabetes. Although it is not the most identified patient related risk factor, the presence of diabetes has been proven to be significantly associated with a risk of PHLF.[30,31]

As demonstrated in several previous studies,[6,29,32] volume does not necessarily correlate with liver function, usually underestimating it. This can be explained by several aspects. First, hepatic function is not preserved homogeneously over the whole liver, this phenomenon is accentuated in case of embolization.[33] Secondly, depending on the mode chosen to calculate FRL, it has been shown that an under- or overestimation of volumes could occur.[32] This is confirmed in the present analyzes, showing significant results for PHLF prediction with HBS function gain and function KGR after embolization, compared to what is observed with volume gain and growth alone.

Multiple surrogates were used and evaluated to predict the risk of PHLF.[17,23,32,34,35] The evaluation of FLR-F and KGR-F was particularly well studied in the setting of the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure.[23] HBS was more accurate than liver volumetry in PHLF prediction following the stage 2 of the ALPPS procedure. Others have highlighted that a kinetic aspect regarding volumetric data could

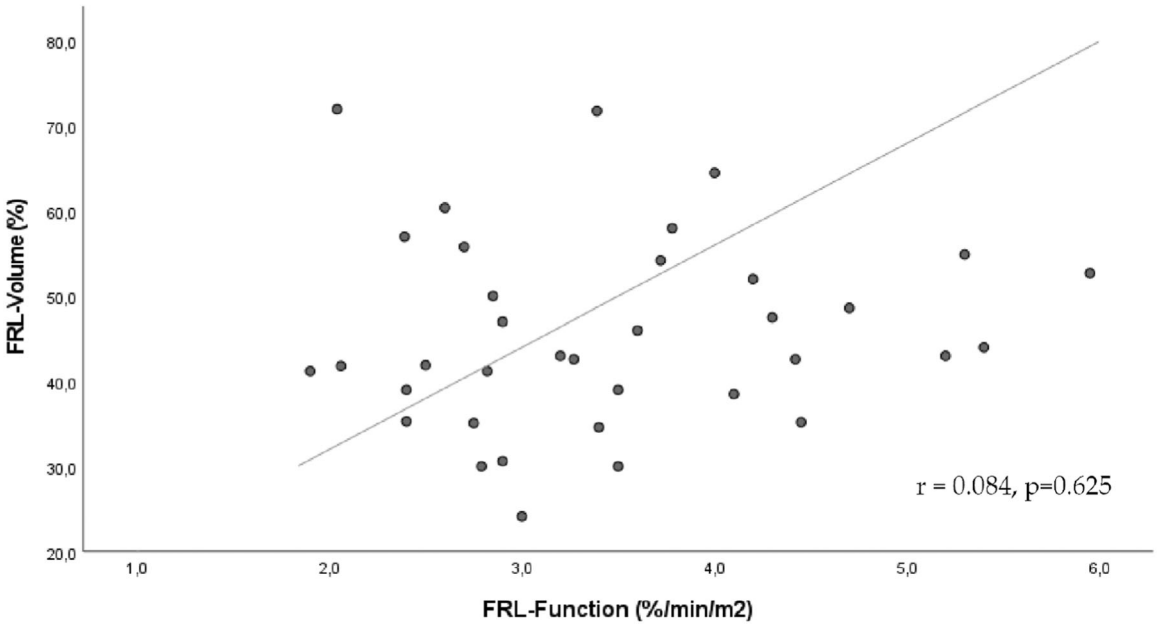

FIGURE 2 Correlation between preoperative future liver function and volume before liver venous manipulations. FRL-V, future remnant liver volume; FRL-F, future remnant liver function.

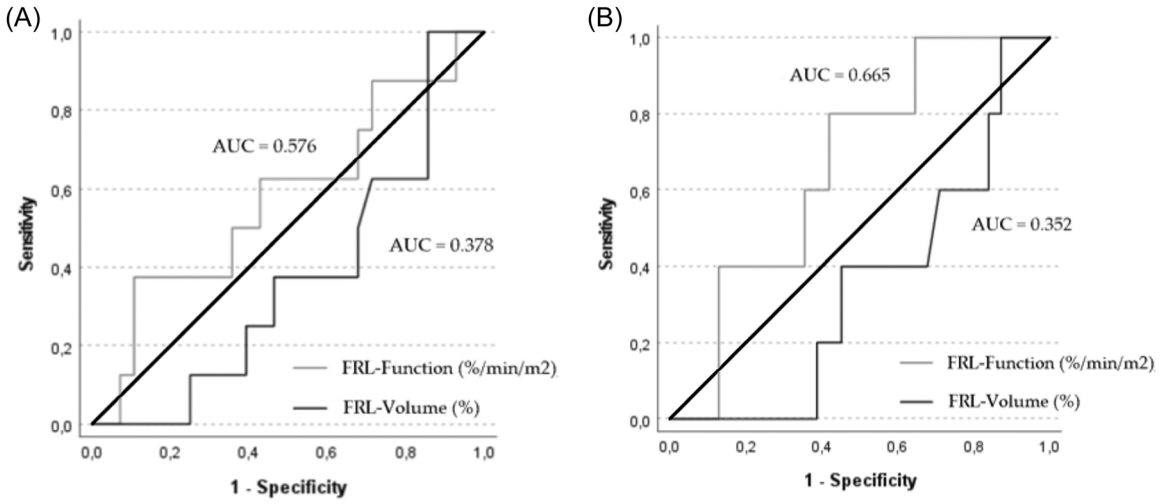

FIGURE 3 Receiver operator characteristic curve analysis of FRL-F and FRL-V in the prediction of liver failure (A: overall; B: grade B and C). FRL-F (%/min/m^2). FRL-V (%). AUC, area under the curve; FRL-F, future remnant liver function; FRL-V, future remnant liver volume;.

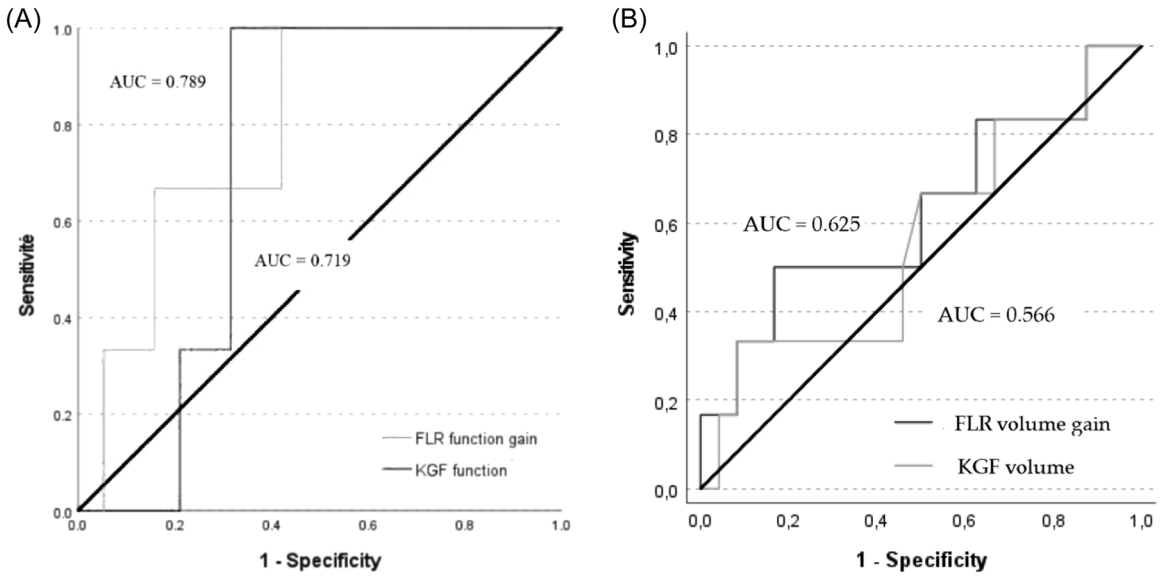

FIGURE 4 Receiver operator characteristic curve analysis of function (A) and volume (B) gain in the prediction of liver failure. (A) FRL function gainKGF function. (B) FRL volume gain. KGF volume. FRL, future remnant liver. KGF, kinetic growth factor.

provide a more accurate evaluation, due to an analysis of the patient-specific kinetic liver growth. But this evaluation was only based on volumetric data.[18] In the present study, the absolute value of FLR function and KGR-V did not significantly predict the occurrence of PHLF. On the other hand, a cut-off value of 150% regarding function gain was identified with a high true positive value and an acceptable specificity in patients undergoing venous manipulation to promote liver hypertrophy before major hepatectomy. This is the first study that demonstrates the importance of function gain and KGR-F with HBS, suggesting that this increase in function may be more accurate to predict PHLF than the preoperative absolute value but is also more accurate than the kinetic analysis based on volumetric evaluations. These findings are particularly important in the setting of venous embolization.

Most of the patients included in the present study required PVE or LVD because of insufficient FLR volume according to a decision algorithm. It has been shown that LVD is a safe procedure,[8,36] owing a better function gain that is correlated with increased postoperative outcomes regarding PHLF occurrence.[9]

This study has some limitations. First, its retrospective design may lead to selection bias. Secondly, planed hepatectomy may be from time to time different from what is effectively done in the operating room, due to anatomical or surgical considerations. To overcome this issue and to correlate postoperative results as much as

possible with the different imaging, a senior physician from the department of nuclear medicine reviewed all the HBS. All liver volumetries were also reassessed by a trainee surgeon and a radiologist.

In conclusion, the present study showed that KGR-F and function gain assessed by HBS after liver venous manipulation predict the risk of developing PHLF after major hepatectomy. The two-time-point evaluation of liver function with HBS seems to be more accurate than its use to assess lobar liver function at a certain time-point. Further larger studies are needed to confirm the pivotal role of kinetic function rate after venous embolization.

ACKNOWLEDGMENTS

Open access funding provided by Universite de Lausanne.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

NA.

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How to cite this article: Smet H, Martin D, Uldry E, et al. Tc-99m mebrofenin hepatobiliary scintigraphy to assess future liver remnant function before major liver surgery. *J Surg Oncol*. 2023;128:1312-1319. doi:10.1002/jso.27426