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MAGNETIC RESONANCE

Predicting liver failure after extended right hepatectomy following right portal vein embolization with gadoxetic acid-enhanced MRI

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Abstract

Objectives Predicting post-hepatectomy liver failure (PHLF) after extended right hepatectomy following portal vein embolization (PVE) from serial gadoxetic acid-enhanced magnetic resonance imaging (MRI).

Methods Thirty-six patients who underwent hepatectomy following PVE were evaluated prospectively with gadoxetic acid-enhanced MRI examinations at predefined intervals during the course of their treatment, i.e., before and 14 days and 28 days after PVE as well as 10 days after hepatectomy. Relative enhancement (RE) and volume of the left and right liver lobes were determined. The study population was divided into two groups with respect to signs of PHLF. Differences between the two groups were assessed using the Mann-Whitney *U* test, and predictive parameters for group membership were investigated using ROC and logistic regression analysis.

Results RE of the left lobe prior to PVE versus 14 days after PVE was significantly lower in patients with PHLF than in those without PHLF (Mann-Whitney *U* test $p < 0.001$) and proved to be the best predictor of PHLF in ROC analysis with an AUC of 0.854 ($p < 0.001$) and a cutoff value of − 0.044 with 75.0% sensitivity and 92.6% specificity. Consistent with this result, logistic linear regression analysis adjusted for age identified the same parameter to be a significant predictor of PHLF ($p = 0.040$).

Conclusions Gadoxetic acid-enhanced MRI performed as an imaging-based liver function test before and after PVE can help to predict PHLF. The risk of PHLF can be predicted as early as 14 days after PVE.

Key Points

- *To predict the likelihood of post-hepatectomy liver failure, it is important to estimate not only future liver remnant volume prior to extended liver resection but also future liver remnant function.*
- *Future liver remnant function can be predicted by performing gadoxetic acid-enhanced MRI as an imaging-based liver function test before and after portal vein embolization.*
- *A reduction of relative enhancement of the liver in gadoxetic acid-enhanced MRI after portal vein embolization of 0.044 predicts post-hepatectomy liver failure with 75.0% sensitivity and 92.6% specificity.*

Keywords Liver · Hepatectomy · Contrast agent · Magnetic resonance imaging

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Abbreviations

ALBI	Albumin-bilirubin
FLR-F	Future liver remnant function
FLR-V	Future liver remnant volume
KGR	Kinetic growth rate
LiMAx	13C-Methacetin breath test
LLL	Left liver lobe
PHLF	Post-hepatectomy liver failure
PVE	Portal vein embolization
RE	Relative enhancement
RLL	Right liver lobe

Introduction

Post-hepatectomy liver failure (PLHF) remains a dreaded complication of extended right hepatectomy as it is a major cause of mortality [1–5]. Efforts to predict the likelihood of PLHF and thereby improve patient selection have been made for decades [5]. Although liver volumetry is routinely used to estimate future liver remnant volume and volume thresholds exist for presumably safe hepatectomy, it is generally recognized that volume is not a perfect surrogate parameter for liver function and hence the likelihood of PLHF, especially not in settings with inhomogeneously distributed liver function such as after portal vein embolization (PVE) [6–8]. Consequently, the foremost aim in this population is to predict future liver remnant function (FLR-F) prior to hepatectomy rather than future liver remnant volume (FLR-V) [9]. While several methods exist to assess global liver function such as laboratory tests to evaluate liver enzymes, clinical and biochemical grading schemes such as the Child-Pugh classification, and the Model for End-Stage Liver Disease (MELD) score or dynamic liver function tests such as the indocyanine green (ICG) plasma disappearance rate and the ^{13}C-methacetin breath test (LIver MAXimum function capacity, LiMAx, Humedics GmbH), these tools fail to account for regional differences in liver function when evaluating FLR-F, as has already been pointed out [9]. Approaches to overcome this predicament involve imaging-based liver function tests such as ^{99m}Tc-labeled mebrofenin scintigraphy combined with single photon emission computed tomography (SPECT) and gadoxetic acid-enhanced magnetic resonance imaging (MRI) [10–12].

The use of gadoxetic acid-enhanced MRI as an imaging-based liver function test has been extensively studied, and its validity has been corroborated in comparison with all of the above-mentioned global liver function tests [13–18]. Parameters derived from gadoxetic acid-enhanced MRI have subsequently been evaluated as predictors of PHLF with some success [19–21].

Furthermore, recent studies have shown that valuable additional information on regional liver function can be obtained through monitoring the reaction of liver parenchyma to PVE reflected by regional changes in gadoxetic acid-enhanced MRI [22, 23]. This observation opens up a new option for predicting FLR-F more accurately. PVE results in a controlled difference in regional liver function, creating an ideal condition to validate gadoxetic acid-enhanced MRI as an imaging-based liver function test and to elucidate the capacity of liver parenchyma to increase its function in such a setting. This study takes advantage of these specific conditions by comparing gadoxetic acid-enhanced MRI scans acquired prospectively before PVE and after PVE. This has only been done in one small retrospective study before [24]. The aim of this explorative study was to identify the parameter derived from serial gadoxetic acid-enhanced MRI scans performed at predefined times during the course of treatment with PVE and hepatectomy that best predicts PHLF.

Methods

Study design and population

Thirty-six consecutive patients who underwent hepatectomy following PVE at our institution between March 2012 and October 2014 were evaluated prospectively by repeated gadoxetic acid-enhanced MRI at predefined times before, during, and after treatment, and their clinical status was monitored and graded according to the PHLF severity grading system of the International Study Group of Liver Surgery. Included were all patients above the age of 18 who had given written informed consent and did not meet any of the exclusion criteria which comprised a glomerular filtration rate under 30 ml/min/1.73 m^2, a pacemaker or other ferromagnetic implant, a previous allergic reaction to gadoxetic acid, mental disorders, claustrophobia, pregnancy, or a previous liver resection. During the course of the study, the number of patients decreased because of retrospectively detected technical errors in one of the MRI scans (sequence parameters (TE) between scans prior to gadoxetic acid administration and those after gadoxetic acid administration were found to differ from each other so that it was not possible to calculate the relative enhancement), not all patients received MRI 28 days after PVE for organizational reasons, and some patients initially considered did not undergo hepatectomy due to extensive tumor progression or peritoneal carcinomatosis. The time course of the study with the number of patients (n) at each time point is illustrated in Fig. 1, and patient characteristics are summed up in Table 1. The study protocol was approved by the institutional review board. Patients received printed information about the study purpose and examinations, and written informed consent was obtained.

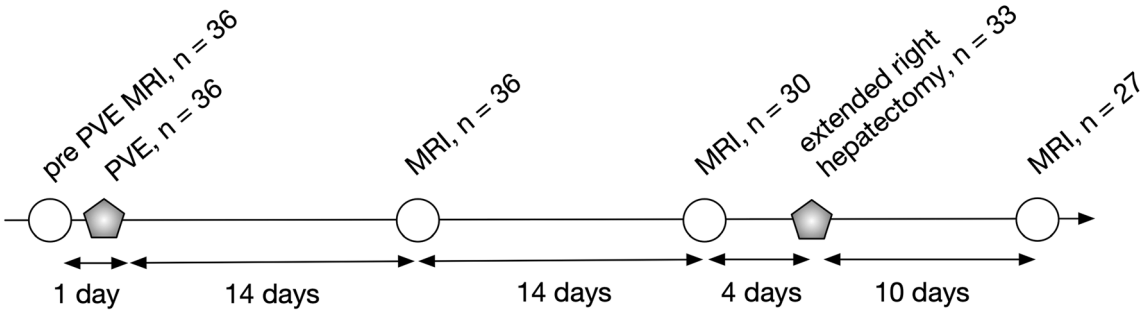

Fig. 1 Time course of the study

PVE and extended right hepatectomy

PVE of the right portal vein was performed as a routine procedure using an ultrasound-guided percutaneous transhepatic access to the right portal vein. After portography to visualize the anatomy, embolization of the right portal vein was performed with particles and coils embolizing segment V–VIII and sparing segment I–IV. Extended right hepatectomy, i.e., resection of segment IV–VIII, was performed approximately 32 days after PVE when the patient still met the prerequisites for the procedure at that time point (see study population).

MRI

Patients underwent gadoxetic acid-enhanced MRI scans before and 14 days and 28 days after PVE as well as 10 days after hepatectomy. All MRI examinations were performed in a 1.5-T Siemens Magnetom Avanto MRI scanner (Siemens Healthcare) using an eight-channel body phased-array coil. Transverse T1-weighted images (volume-interpolated breath-hold examination (VIBE) sequence with the following parameters: repetition time (TR) of 4.26 ms, echo time (TE) of 1.93 ms, flip angle of 30°, slice thickness of 3 mm, and matrix size of 256 × 127 covering the entire liver with 60–80 slices and an adjusted field of view of 255–300 × 340–400 mm) were acquired before and 20 min after manual IV bolus injection of 0.1 ml per kg body weight of Gd-EOB-DTPA (Primovist, Bayer Pharma).

Image analysis

Images were analyzed using the Visage 7.1.4 software (Visage Imaging). Signal intensity (SI) was measured by two independent readers (clinical radiologists with 9 and 7 years of abdominal MRI experience) in three regions of interest (ROIs) with approximately 2.5 cm diameter within the left liver lobe (LLL) and within the right liver lobe (RLL) prior to ($SI_{unenhanced}$) and 20 min after IV bolus injection of gadoxetic acid ($SI_{20\ min}$). The two readers placed the ROIs, avoiding large vessels, bile ducts, and tumor masses. The readers were blinded with regard to clinical outcome, i.e., whether the patients developed PHLF or not. Figure 2 presents an example of these measurements. Relative enhancement (RE) was calculated with the following formula:

$$RE = (SI_{20\ min} - SI_{unenhanced}) / SI_{unenhanced}$$

The results of the two readers were averaged, and interrater reliability was estimated with the two-way mixed, average measure intraclass correlation coefficient (ICC).

Liver volumes were determined by manual delineation of the liver borders excluding large vessels, bile ducts, and tumor masses. Right and left liver lobe volumes were determined from the input of the liver surgeons performing the resection as well as the difference in enhancement after PVE ("demarcation line") and transferring the resection line to images acquired prior to PVE. The kinetic growth rate (KGR) was calculated according to Shindoh et al [25]: KGR = degree of hypertrophy at post-PVE volume assessment (%)/time (in weeks) elapsed since PVE at post-PVE volume assessment.

PHLF

Relative severity of post-hepatectomy liver failure (PHLF) was assessed retrospectively using the consensus definition and severity grading system of the International Study Group of Liver Surgery (ISGLS) published by Rahbari et al [2]. The study group graded PHLF into three categories: grade A, defined as "PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient" [2]; grade B, defined as "PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment" [2]; and grade C, defined as "PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment" [2].

For analysis, the study population was first divided into two groups: patients who developed PHLF according to the ISGLS definition and those who did not. Subsequently, the study population was divided into two groups using different criteria to separate patients: patients who developed severe PHLF (corresponding to grade C) versus those with mild (grade A or B) or no PHLF.

Table 1 Descriptive statistics of the study population and comparison of subgroups using the Mann-Whitney *U* test

Parameter	All	No PHLF	PHLF	MWU *p* value	No/mild PHLF	Severe PHLF	MWU *p* value
Baseline number°	36	22 (61.1%)	14 (38.9%)	–	28 (77.8%)	8 (22.2%)	–
Age (years)	62 (± 10.8)	57 (± 9.7)	69 (± 8.6)	0.002*	60 (± 10.4)	68 (± 10.3)	0.062
Height (cm)	172 (± 8.6)	172 (± 8.1)	171 (± 9.6)	0.615	172 (± 8.7)	173 (± 8.8)	0.775
Body weight (kg)	75 (± 13.7)	74 (± 11)	76 (± 17)	0.897	73 (± 12)	79 (± 19)	0.518
Reason for hemihepatectomy							
Colorectal liver metastasis	11 (30.6%)	8 (36.4%)	3 (21.4%)	–	9 (32.1%)	2 (25.0%)	–
Hilar cholangiocarcinoma	11 (30.6%)	4 (18.2%)	7 (50.0%)	–	7 (25.0%)	4 (50.0%)	–
Hepatocellular carcinoma (HCC)	1 (2.8%)	1 (4.5%)	0 (0.0%)	–	1 (3.6%)	0 (0.0%)	–
Cholangiocellular carcinoma (CCC)	5 (13.9%)	3 (13.6%)	2 (14.3%)	–	4 (14.3%)	1 (12.5%)	–
Focal nodular hyperplasia (FNH)	1 (2.8%)	1 (4.5%)	0 (0.0%)	–	1 (3.6%)	0 (0.0%)	–
Other	7 (19.4%)	5 (22.7%)	2 (14.3%)	–	6 (21.4%)	1 (12.5%)	–
Duration of surgery (min)	307 (± 104)	318 (± 96)	290 (± 119)	0.811	291 (± 110)	354 (± 71)	0.101
Intensive care unit time (days)	5.7 (± 15.3)	2.2 (± 2.5)	11.8 (± 24.6)	0.047*	2.1 (± 2.3)	17 (± 29)	0.087
Time PVE to hepatectomy (days)	28.1 (± 6.3)	28.2 (± 6.5)	28.0 (± 6.0)	0.952	28.9 (± 6.6)	26.0 (± 5.0)	0.245
Bilirubin prior to PVE (mg/dl)	1.2 (± 1.4)	1.3 (± 1.7)	1.1 (± 1.0)	0.557	1.2 (± 1.5)	1.3 (± 1.3)	0.745
ALBI score value prior to PVE ($n = 36$)	− 2.64 (± 0.50)	− 2.70 (± 0.53)	− 2.53 (± 0.46)	0.227	− 2.64 (± 0.51)	− 2.62 (± 0.52)	0.808
ALBI score value post PVE ($n = 27$)	− 2.5 (± 0.54)	− 2.69 (± 0.51)	− 2.36 (± 0.54)	0.075	− 2.57 (± 0.53)	− 2.48 (± 0.63)	0.766
Total liver volume (TLV) prior to PVE (ml)	1790 (± 412)	1826 (± 469)	1799 (± 589)	0.685	1774 (± 443)	1960 (± 719)	0.718
KGR prior to vs 14 days post PVE (%)	14.0 (± 10.0)	16.1 (± 11.0)	10.5 (± 7.0)	0.057	15.2 (± 10.6)	9.5 (± 5.2)	0.184
KGR prior to vs 28 days post PVE (%)	8.7 (± 4.9)	9.3 (± 4.6)	7.9 (± 5.4)	0.157	9.4 (± 5.3)	6.3 (± 2.6)	0.086
KGR 14 days vs 28 days post PVE (%)	3.5 (± 3.5)	2.2 (± 2.8)	5.2 (± 3.7)	0.059	3.2 (± 3.4	4.3 (± 3.8)	0.773
LiMAx prior to PVE (μg/h/kg)	425 (± 115)	444 (± 124)	391 (± 90)	0.220	434 (± 117)	394 (± 108)	0.509
LiMAx 14 days post PVE (μg/h/kg)	461 (± 159)	496 (± 179)	405 (± 102)	0.068	468 (± 170)	435 (± 116)	0.624
LiMAx 1 day hepatectomy (μg/h/kg)	148 (± 44)	148 (± 46)	150 (± 43)	0.978	146 (± 45)	154 (± 44)	0.643
LLL volume seg. 2 and 3 prior to PVE	371 (± 127)	371 (± 121)	370 (± 140)	0.737	373 (± 130)	361 (± 131)	0.614
LLL volume seg. 2 and 3 14 days post PVE	485 (± 146)	500 (± 139)	461 (± 159)	0.133	493 (± 152)	457 (± 130)	0.399
LLL volume seg. 2 and 3 28 days post PVE	504 (± 143)	514 (± 129)	487 (± 166)	0.180	516 (± 146)	460 (± 132)	0.168
LLL volume seg. 2 and 3 increase prior to vs 14 days post PVE	1.34 (± 0.19)	1.38 (± 0.20)	1.27 (± 0.16)	0.116	1.35 (± 0.20)	1.30 (± 0.16)	0.588
LLL volume seg. 2 and 3 increase prior to vs 28 days post PVE	1.40 (± 20)	1.43 (± 0.21)	1.35 (± 0.19)	0.267	1.42 (± 0.20)	1.32 (± 0.21)	0.193
LLL volume seg. 2–4 prior to PVE	666 (± 172)	649 (± 138)	692 (± 219)	0.810	651 (± 161)	716 (± 211)	0.588
LLL volume seg. 2–4 14 days post PVE	821 (± 194)	848 (± 189)	776 (± 202)	0.148	834 (± 203)	768 (± 158)	0.427
LLL volume seg. 2–4 28 days post PVE	856 (± 196)	860 (± 171)	849 (± 237)	0.377	858 (± 190)	849 (± 232)	0.668
LLL volume seg. 2–4 increase prior to vs 14 days post PVE	1.26 (± 0.17)	1.31 (± 0.17)	1.19 (± 0.15)	0.012*	1.29 (± 0.17)	1.16 (± 0.11)	0.073
LLL volume seg. 2–4 increase prior to vs 28 days post PVE	1.31 (± 0.17)	1.34 (± 0.17)	1.25 (± 0.15)	0.057	1.34 (± 0.17)	1.20 (± 0.10)	0.019*
FLRV prior to PVE (ml)	0.21 (± 0.05)	0.20 (± 0.05)	0.21 (± 0.06)	0.885	0.21 (± 0.05)	0.19 (± 0.04)	0.378
FLRV prior to hepatectomy (ml)	0.28 (± 0.06)	0.29 (± 0.06)	0.27 (± 0.07)	0.343	0.29 (± 0.58)	0.25 (± 0.06)	0.077
Increase in FLR	1.40 (± 0.17)	1.44 (± 0.18)	1.33 (± 0.12)	0.066	1.42 (± 0.17)	1.35 (± 0.16)	0.284
FLRV prior to hepatectomy/TLV prior to PVE	0.17 (± 0.06)	0.17 (0.06)	0.16 (± 0.06)	0.860	0.18 (± 0.06)	0.14 (± 0.06)	0.207
LLL RE prior to PVE	0.62 (± 0.14)	0.62 (± 0.16)	0.62 (± 0.10)	0.752	0.61 (± 0.14)	0.63 (± 0.11)	1.000
LLL RE 14 days post PVE	0.67 (± 0.16)	0.72 (± 0.17)	0.59 (± 0.11)	0.002*	0.70 (± 0.16)	0.57 (± 0.12)	0.030*
LLL RE 28 days post PVE	0.70 (± 0.18)	0.76 (± 0.18)	0.61 (± 0.14)	0.014*	0.73 (± 0.18)	0.58 (± 0.10)	0.042*

Table 1 (continued)

Parameter	All	No PHLF	PHLF	MWU *p* value	No/mild PHLF	Severe PHLF	MWU *p* value
LLL RE post hepatectomy	0.48 (± 0.21)	0.53 (0.22)	0.32 (± 0.10)	0.007*	0.52 (± 0.22)	0.34 (± 0.09)	0.029*
Increase in LLL RE prior vs 14 days post	0.17 (± 44)	0.31 (± 0.51)	− 0.05 (± 0.11)	< 0.001*	0.24 (± 0.47)	− 0.09 (± 0.09)	0.001*
Increase in LLL RE prior vs 28 days post	0.27 (± 59)	0.47 (± 0.72)	0.01 (± 0.18)	0.001*	0.36 (± 0.65)	− 0.03 (± 0.10)	0.003*
RLL RE prior to PVE	0.64 (± 0.19)	0.66 (± 0.22)	0.61 (± 0.13)	0.372	0.65 (± 0.20)	0.61 (± 0.15)	0.479
RLL RE 14 days post PVE	0.49 (± 0.16)	0.52 (± 0.17)	0.44 (± 0.13)	0.109	0.50 (± 0.15)	0.45 (± 0.16)	0.399
RLL RE 28 days post PVE	0.50 (± 0.14)	0.53 (± 0.16)	0.44 (± 0.09)	0.082	0.53 (± 0.14)	0.40 (± 0.08)	0.019*

Descriptives of metric variables are given as mean (±standard deviation); categorical parameters are described by absolute and relative proportions

PHLF post-hepatectomy liver failure, *ALBI* albumin-bilirubin, *LiMAx* 13C-methacetin breath test, *RLL* right liver lobe, *LLL* left liver lobe, *RE* relative enhancement, *PVE* portal vein embolization, *KGR* kinetic growth rate, *FLRV* future liver remnant volume

°For the numbers in follow-up examinations, compare with case numbers (*n*) indicated in Fig. 1 depicting the time course of the study and the numbers (*N*) shown in further statistical analysis (Tables 2 and 3 and Fig. 3a, b)

*Denotes $p < 0.05$ which is considered statistically significant

In addition to that, the available laboratory values of the patients including bilirubin and albumin were gathered before and after PVE and the so-called albumin-bilirubin (ALBI) score was calculated according to Johnson et al using the following formula [26]: ALBI score = 0.66 × log10 (total bilirubin [μmol/L]) − 0.085 × (albumin [g/L]). Furthermore, the available ^{13}C-methacetin LiMAx (maximum liver function capacity) test results before and after PVE were gathered [27].

Descriptive statistics of the study population and comparison of subgroups obtained with the Mann-Whitney *U* test are summarized in Table 1.

Statistics

Continuous variables are presented as mean ± standard deviation (SD). Differences between two groups were assessed with the Mann-Whitney *U* (MWU) test. Receiver operating characteristic (ROC) analysis was performed to identify the best predictor of PHLF/severe PHLF. DeLong's test was used to elucidate statistically significant differences between the ROC curves. Univariate and multivariate linear logistic regression analysis was performed to verify the results when adjusted for different age distribution in subgroups. Interrater reliability was estimated with the two-way mixed, average measure intraclass correlation coefficient (ICC).

All statistical analysis was performed using SPSS Statistics 23 (IBM) or R 3.5.1 (R Foundation for Statistical Computing). A p value of < 0.05 was considered statistically significant. According to the explorative character of this study with focus on development of hypothesis we decided to perform no adjustment for multiple comparisons which would be favorable in a confirmative analysis.

Results

Analysis of interrater reliability of the two independent radiologists who measured liver signal intensities in our study yielded an intraclass correlation coefficient of 0.989 for all measurements pooled and values of > 0.90 in all subgroup analyses, indicating excellent reliability.

A comparison of patients who did not develop PHLF with those who did revealed a statistically significant difference in RE of the LLL at 14 and 28 days after PVE as well as after hepatectomy, and the corresponding increase in RE of the LLL before versus 14 days and 28 days after PVE was significantly lower in patients with PHLF than in those without PHLF (MWU test $p = 0.002$, $p = 0.014$, $p < 0.001$ and 0.001, respectively; see Table 1). An increase in LLL volume before and 14 days after PVE as well as mean age was also significantly different between the two groups (MWU test $p = 0.012$, $p = 0.047$, and $p = 0.002$, respectively; see Table 1).

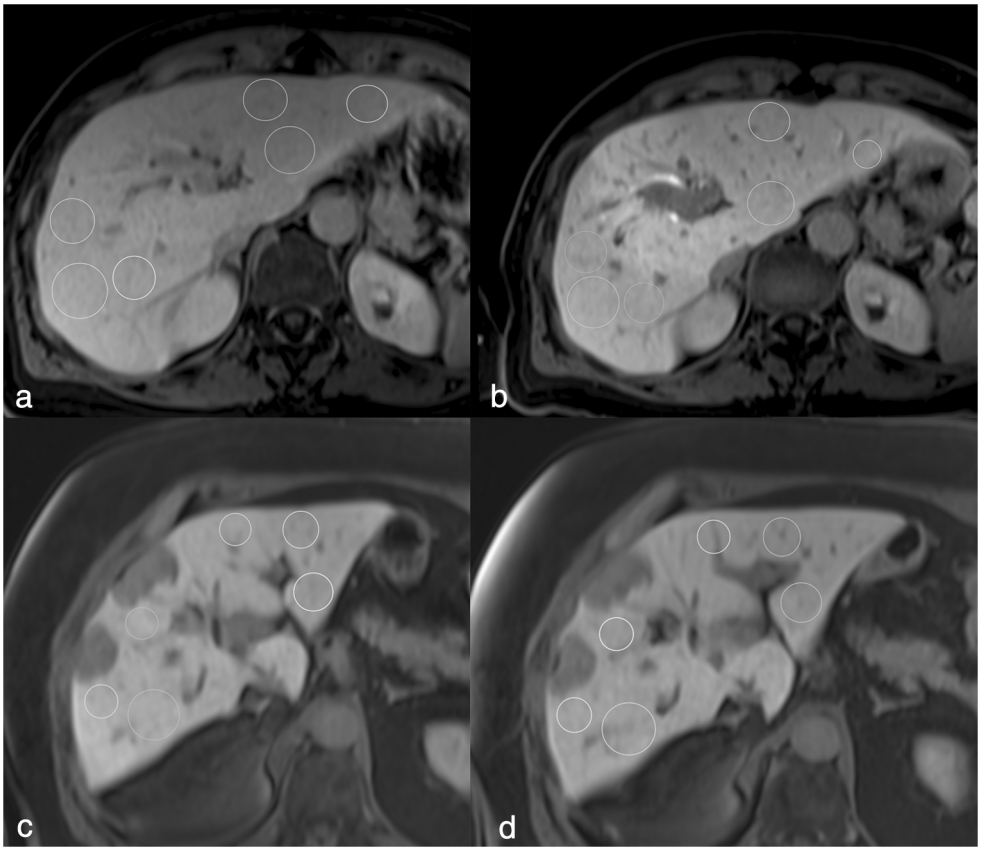

Fig. 2 Gadoxetic acid-enhanced MR images of two patients before and 14 days after portal vein embolization (PVE): the patient in the first row with hilar cholangiocarcinoma, who did not develop post-hepatectomy liver failure (PHLF), showing increased relative enhancement (RE) of the left liver lobe after PVE (**a** and **b**); in contrast, there is no increased RE in the patient with colorectal liver metastases presented in the second row (**c** and **d**), who developed PHLF. The circles in the MR images illustrate regions of interest (ROI) placed to measure signal intensity

Similar results were found when comparing patients with no or mild PHLF versus those with severe PHLF: there were statistically significant differences in RE of the LLL at 14 and 28 days after PVE as well as after hepatectomy and an increase in RE of the LLL before versus 14 days and 28 days after PVE (MWU test $p = 0.030$, $p = 0.042$, $0 = 0.029$, $p = 0.001$, $p = 0.003$, respectively; see Table 1). However, there was a slight difference to the results for patients without versus those with PHLF in that the increase in LLL volume before and 28 days after PVE and RE of the RLL 28 days after PVE differed significantly between patients with no or mild PHLF and those with severe PHLF (MWU test $p = 0.019$, $p = 0.019$, respectively; see Table 1).

In the ROC analysis performed to identify the parameter most suitable to predict PHLF or severe PHLF ROC, already established biochemical tools such as the ALBI score and the LiMAx test proved to be no statistically significant predictors, while amongst the parameters that were shown to be statistically significant predictors, the RE of the LLL prior to PVE versus 14 days after PVE was found to have the greatest area under the curve (AUC = 0.854, $p < 0.001$, for the former and AUC = 0.880, $p < 0.001$, for the latter; see Tables 2 and 3 and Fig. 3a, b). This indicates that RE of the LLL prior to PVE versus 14 days after PVE is the best predictor of both PHLF and severe PHLF. As expected, RE of the LLL at 14 and 28 days after PVE as well as after hepatectomy and the increase in RE of the LLL before versus 14 and 28 days after PVE were also statistically significant predictors of PHLF and severe PHLF in ROC analysis (Tables 2 and 3, Fig. 3a, b), and while having smaller AUCs, the differences between the ROC curves were not significant when tested with DeLong test.

Consistent with the results of the comparison of means with the MWU test, RE of the RLL prior to PVE versus 28 days after PVE was also found to be a statistically significant predictor of severe PHLF (Table 3).

For the prediction of PHLF, a cutoff of − 0.044 in RE of the LLL prior to PVE versus 14 days after PVE was identified, yielding 75.0% sensitivity and 92.6% specificity. For prediction of severe PHLF, a cutoff of 0.051 in RE of the LLL prior to PVE versus 14 days after PVE was identified, yielding 92.9% sensitivity and 71.4% specificity (Table 4).

In accordance with the ROC analysis, the increase in RE of the LLL prior to PVE versus 14 days after PVE proved to be a statistically significant parameter in logistic regression analysis, predicting PHLF and severe PLHF with a p value of 0.009 for the latter and a p value of 0.023 for the former (Table 5). This was also the case when the analysis was adjusted for differences in age distribution, the only possible confounder

Table 2 ROC analysis: PHLF versus no PHLF

Predictive parameter of PHLF	*N*	AUC	*p* value
Left liver			
RE prior to PVE	35	0.534	0.752
RE 14 days post PVE	36	0.805	0.002*
RE 28 days post PVE	30	0.765	0.014*
RE post hepatectomy	27	0.850	0.007*
Increase in RE prior vs 14 days post	35	0.854	< 0.001*
Increase in RE prior vs 28 days post	29	0.841	0.002*
Right liver			
RE prior to PVE	35	0.592	0.372
RE 14 days post PVE	36	0.662	0.109
RE 28 days post PVE	30	0.690	0.082
ALBI score value prior to PVE	36	0.623	0.218
ALBI score value post PVE	27	0.703	0.075
LiMax value prior to PVE	34	0.631	0.099
LiMAx value post PVE	34	0.690	0.093
LLL volume seg. 2 and 3 increase prior to vs 14 days post PVE	36	0.659	0.112
LLL volume seg. 2 and 3 increase prior to vs 28 days post PVE	36	0.614	0.256
LLL volume seg. 2–4 increase prior to vs 14 days post PVE	34	0.758	0.012*
LLL volume seg. 2–4 increase prior to vs 28 days post PVE	36	0.692	0.056
Increase in FLR	36	0.685	0.064
FLRV prior to hepatectomy/TLV prior to PVE	36	0.481	0.846

ROC AUC was analyzed using Mann-Whitney *U* test

PHLF post-hepatectomy liver failure, *RE* relative enhancement, *PVE* portal vein embolization, *RLL* right liver lobe, *LLL* left liver lobe, *RE* relative enhancement, *ALBI* albumin-bilirubin, *LiMAx* 13C-methacetin breath test

*Denotes $p < 0.05$ which is considered statistically significant

Table 3 ROC analysis: severe PHLF versus no or mild PHLF

Predictive parameter of severe PHLF	*N*	AUC	*p* value
Left liver			
RE prior to PVE	35	0.500	1.000
RE 14 days post PVE	36	0.754	0.030*
RE 28 days post PVE	30	0.758	0.042*
RE post hepatectomy	27	0.802	0.029*
Increase in RE prior vs 14 days post	35	0.880	< 0.001*
Increase in RE prior vs 28 days post	29	0.864	0.005*
Right liver			
RE prior to PVE	35	0.586	0.586
RE 14 days post PVE	36	0.603	0.399
RE 28 days post PVE	30	0.801	0.019*
ALBI score value prior to PVE	36	0.529	0.805
ALBI score value post PVE	27	0.539	0.761
LiMax value prior to PVE	34	0.585	0.496
LiMAx value post PVE	34	0.563	0.609
LLL volume seg. 2 and 3 increase prior to vs 14 days post PVE	36	0.567	0.568
LLL volume seg. 2 and 3 increase prior to vs 28 days post PVE	36	0.656	0.183
LLL volume seg. 2–4 increase prior to vs 14 days post PVE	34	0.725	0.070
LLL volume seg. 2–4 increase prior to vs 28 days post PVE	36	0.772	0.020*
Increase in FLR	36	0.629	0.110
FLRV prior to hepatectomy/TLV prior to PVE	36	0.652	0.196

ROC AUC was analyzed using Mann-Whitney *U* test

PHLF post-hepatectomy liver failure, *RE* relative enhancement, *PVE* portal vein embolization, *RLL* right liver lobe, *LLL* left liver lobe, *RE* relative enhancement, *ALBI* albumin-bilirubin, *LiMAx* 13C-methacetin breath test

*Denotes $p < 0.05$ which is considered statistically significant

found in the comparison of subgroup patient characteristics, with $p = 0.040$ and $p = 0.019$, respectively (Table 5).

Discussion

While the value of gadoxetic acid-enhanced MRI as an imaging-based liver function test is widely recognized, parameters derived from it to predict PHLF are still being investigated [19–21]. The more recent observation that valuable additional information on regional liver function can be obtained through monitoring changes in gadoxetic acid-enhanced MRI that reflect the reaction of liver parenchyma to stress imposed by portal vein embolization (PVE) has opened up a new approach to the prediction of PHLF [23]. In the study presented here, we systematically investigated the additional information acquired by serial MRI in the course of PVE and hepatectomy to identify the parameter that best predicts PHLF and found that the risk of PHLF can be predicted as early as 14 days after PVE with gadoxetic acid-enhanced MRI performed as an imaging-based liver function test before and after PVE by determining relative enhancement of the liver. We elucidated a cutoff value of 0.044 reduction in relative enhancement of the liver after PVE to predict PHLF with 75.0% sensitivity and 92.6% specificity. There is one previous study by Sato et al evaluating MRI-based liver function conducted on PVE patients using the actual incidence of PHLF as the outcome parameter [24]. However, their study is retrospective and the part of the study analyzing the impact of relative enhancement of the liver before and after PVE on the likelihood of PHLF only includes 11 patients with primary liver tumors not further specified.

In our study, comparison of patients who did not develop PHLF with those who did revealed no statistically significant

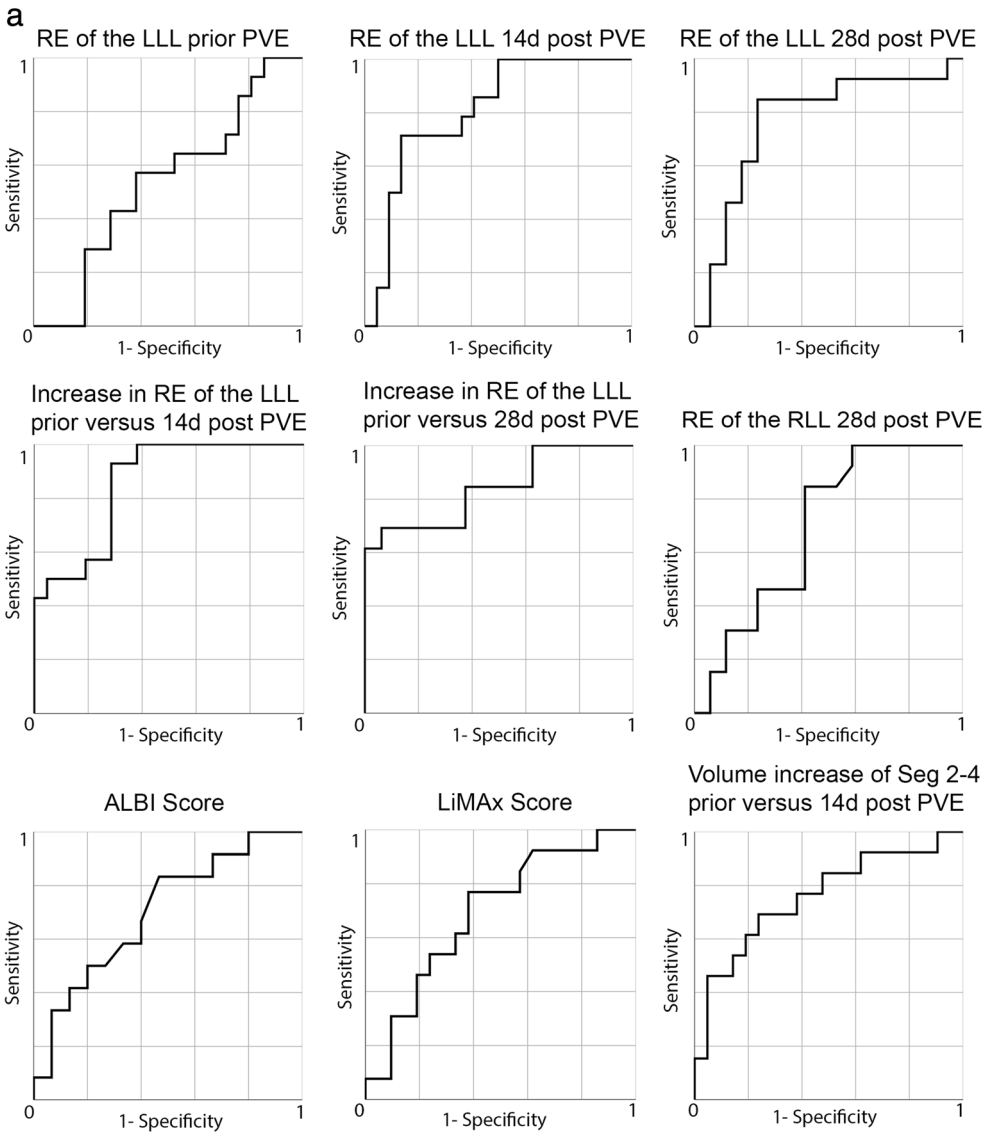

Fig. 3 **a** ROC analysis of parameters derived from gadoxetic acid-enhanced MRI before and after portal vein embolization (PVE) to identify the parameter best predicting post-hepatectomy liver failure (PHLF). RE, relative enhancement; RLL, right liver lobe; LLL, left liver lobe; RE, relative enhancement; ALBI, albumin-bilirubin; LiMAx, 13C-methacetin breath test. **b** ROC analysis of parameters derived from gadoxetic acid-enhanced MRI before and after portal vein embolization (PVE) to identify the parameter best predicting severe post-hepatectomy liver failure (PHLF). RE, relative enhancement; RLL, right liver lobe; LLL, left liver lobe; ALBI, albumin-bilirubin; LiMAx, (3C-methacetin breath test

difference in RE of the LLL or RLL prior to PVE, which is in accordance with the results of Chuang et al but disagrees with the findings reported by Kim et al [20, 21]. A possible reason why Kim et al obtained different results is that they only included patients with hepatocellular carcinoma (HCC), making a higher rate of underlying chronic liver disease more likely. Moreover, the overall rate of PHLF was consecutively higher in their study population, and PVE was not performed. Our study, on the other hand, revealed a statistically significant difference in RE of the LLL at 14 and 28 days after PVE as well as after hepatectomy, and the corresponding increase in RE of the LLL before versus 14 days and 28 days after PVE was found to be significantly lower in patients with PHLF than in those without PHLF. This is in accordance with the results of the above-mentioned study by Sato et al [24] and simply confirms the assumption that the better the liver function of the remaining LLL after PVE, the greater the uptake of gadoxetic acid and hence the greater the RE. Notably, though, the capacity of liver parenchyma to increase its function, i.e., the functional reserve, could not be deduced from a single gadoxetic acid-enhanced MRI prior to PVE alone but was only apparent in repeat MRI scans acquired after PVE. This is paralleled by the fact that imaging prior to PVE does not allow prediction of whether the likely amount of LLL hypertrophy will suffice to compensate for the loss of parenchyma resulting from hepatectomy [23].

Of all parameters investigated in this study, RE of the LLL prior to PVE versus 14 days after PVE had the greatest area under the curve in ROC analysis indicating that this is the best predictor of PHLF and severe PHLF alike. This was confirmed in logistic regression analysis even when adjusted for differences in age distribution in the subgroups. RE-derived MRI parameters were shown to be superior to the evaluated global liver function tests LiMAx and ALBI score. This can be explained by the fact that these global tests cannot distinguish between the embolized and not-embolized parts of the

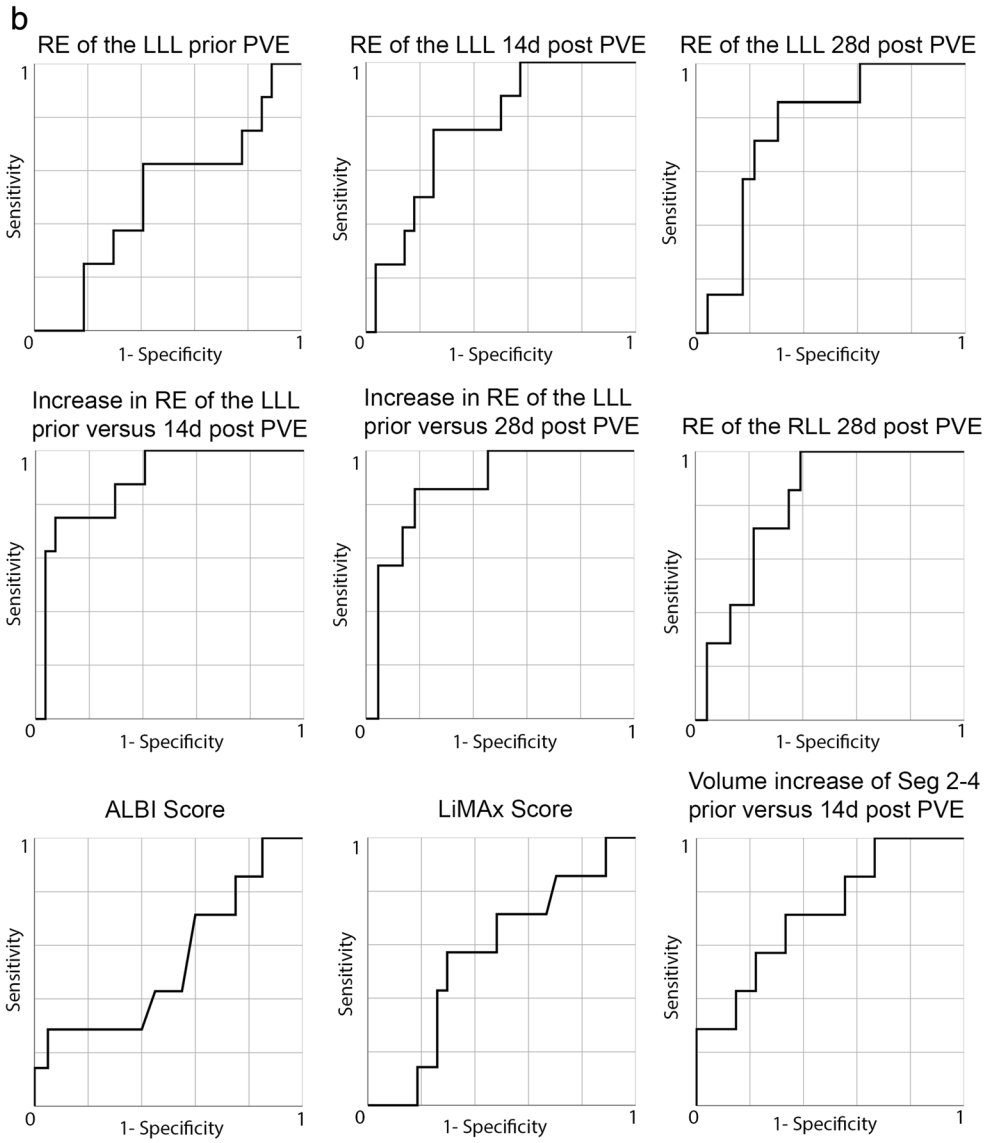

Fig. 3 (continued)

liver but rather give an "average" value for the total liver while the RE-derived MRI parameters can assess the left and right liver lobe separately and in addition to that—by incorporating serial MRI examination—provide information about the capability of regeneration and the functional reserve of the future liver remnant. However, RE of the LLL at 14 and 28 days after PVE as well as after hepatectomy and the increase in RE of the LLL before versus 14 and 28 days after PVE were also statistically significant predictors of PHLF and severe PHLF in ROC analysis and did not differ significantly when tested with the DeLong test. A larger study population is needed to validate the superiority of RE of the LLL prior to PVE versus 14 days after PVE over the other parameters.

Interestingly, we found RE of the RLL 28 days after PVE to be significantly lower in patients who developed severe PHLF. A possible explanation for this rather unexpected finding might be that the more impaired the liver parenchyma is, the more likely its function deteriorates with a loss of portal venous blood supply. In other words, unimpaired liver parenchyma can compensate for the loss of portal venous blood

Table 4 ROC analysis: cutoff of the predictive parameter increase in RE prior to versus 14 days post PVE with respect to PHLF and severe PHLF

Increase in RE of the left lobe prior to versus 14 days post PVE	AUC	Cutoff	Sensitivity	Specificity
Predicting PHLF	0.854	− 0.044	75.0%	92.6%
Predicting severe PHLF	0.880	0.051	92.9%	71.4%

RE relative enhancement, *PVE* portal vein embolization, *PHLF* post-hepatectomy liver failure

Table 5 Univariate and multivariate linear logistic regression analysis of parameters implicated in the likelihood of PHLF and severe PHLF

Predictive parameter	*N*	PHLF		Severe PHLF	
		Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Univariate analysis					
Left liver					
RE prior to PVE	35	1.149 (0.007–185.637)	0.957	2.201 (0.005–925.356)	0.798
RE 14 days post PVE	36	0.001 (0.0–0.419)	0.023*	0.006 (0.0–1.556)	0.071
RE 28 days post PVE	30	0.002 (0.0–0.533)	0.029*	0.002 (0.0–1.528)	0.067
RE post hepatectomy	27	0.003 (0.0–0.745)	0.039*	0.011 (0.0–1.915)	0.086
Increase in RE prior vs 14 days post	35	0.001 (0.0–0.102)	0.023*	0.001 (0.0–0.020)	0.009*
Increase in RE prior vs 28 days post	29	0.001 (0.0–0.462)	0.028*	0.001 (0.0–1.048)	0.051
Right liver					
RE prior to PVE	35	0.239 (0.006–10.189)	0.454	0.295 (0.004–22.432)	0.580
RE 14 days post PVE	36	0.03 (0.0–4.729)	0.176	0.138 (0.001–32.763)	0.477
RE 28 days post PVE	30	1.139 (1.042–1.246)	0.004	0.001 (0.0–0.599)	0.039
Age	36	1.139 (1.042–1.246)	0.004*	1.088 (0.994–1.190)	0.066
Multivariate analysis					
Increase in left liver RE prior vs 14 days post	35	0.001 (0.0–0.218)	0.040*	0.0 (0.0–0.044)	0.019*
Age	35	1.322 (1.038–1.682)	0.023*	1.126 (0.965–1.314)	0.131

Univariate and multivariate analysis of parameters predicting post-hepatectomy liver failure (PHLF) and severe PHLF

RE relative enhancement, *PVE* portal vein embolization

*Denotes $p < 0.05$ which is considered statistically significant

supply while impaired liver parenchyma cannot, which is reflected by a greater decrease in RE after PVE of the latter. Assuming the degree of parenchymal impairment of the LLL is similar to that of the RLL, patients with a greater decrease in RE of the RLL 28 days after PVE are more likely to develop severe PHLF as their LLL also has a greater propensity to deteriorate in function when exposed to the intraoperative stress that hepatic pedicle clamping entails [28, 29].

Besides the described changes in RE, liver volume was assessed during the course of treatment and revealed that the increase in LLL volume before and 14 days after PVE was significantly lower in patients who developed PHLF than in those who did not as described in previous studies [23]. Contrary to that, the subgroup analysis of severe PHLF compared to no or mild PHLF only showed a significant increase in LLL volume before and 28 days after PVE. However, relatively low occurrence of severe PHLF compared to no or mild PHLF renders the result of this subgroup analysis less reliable than the comparison of PHLF versus no PHLF, in which subgroups had a more similar size (Table 1).

Focusing on the more evenly distributed subgroup analysis of PHLF versus no PHLF, we can conclude that relevant changes in RE and LLL volume take place within the first 14 days after PVE, confirming that it may be feasible to perform hepatectomy earlier after PVE than in current standard practice. This finding is in accordance with previous studies and is of relevance as earlier resection might help to minimize tumor progression, not only because it leaves the tumor less time to grow but also because PVE itself has been implicated in stimulating tumor progression [23, 30, 31].

Our study has several limitations. First, we investigated a rather small population size with a relatively low proportion of patients with severe PHLF compared to no or mild PHLF, which renders the result of this subgroup analysis less reliable than the comparison of PHLF versus no PHLF, where cases were fairly evenly distributed. Secondly, our results are based on signal intensity measurements of gadoxetic acid-enhanced MRI rather than the arguably more reproducible T1 mapping method [32–35]. On the other hand, it is advantageous, though, that our results demonstrate validity of signal intensity measurements rather than relying on the less universally available T1 mapping method. A further limitation of the study might the relative lack of patients with HCC included which is probably due to the fact that the majority of patients with HCC either already have multifocal manifestation of the disease or have severely impaired liver function preventing them from undergoing extended right hepatectomy. And lastly, the potential impact of renal impairment on gadoxetic acid-

enhanced MRI was not accounted for nor that of bilirubin interference with gadoxetic acid uptake, although bilirubin levels did not differ significantly from each other in the subgroups we compared in our analysis [36].

In conclusion, gadoxetic acid-enhanced MRI performed as an imaging-based liver function test before and after PVE can help to predict PHLF. The risk of PHLF can be predicted as early as 14 days after PVE.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dominik Geisel.

Conflict of interest Drs Geisel, Hamm, and Denecke have received travel support and honoraria from Bayer AG.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all patients in this study.

Ethical approval Institutional review board approval was obtained.

Study subjects or cohorts overlap The 36 patients included in the current study have already been the subject of an earlier report [23]. The prior study investigated the increase in liver volume and the potential of gadoxetic acid-enhanced MRI to predict the volume increase and monitor the functional increase of the future liver remnant after portal vein embolization. With a longer observation period until the point well after extended hemihepatectomy following portal vein embolization and newly available information of the outcome of surgery and clinical status afterwards, the focus of the current study is on clinical outcome and means of predicting this outcome using several functional parameters including gadoxetic acid-enhanced MRI.

Methodology
- prospective study
- diagnostic or prognostic study
- performed at one institution

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