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EARLY ASSESSMENT OF LIVER FUNCTIONAL RESERVE WITH GD-EOB-DTPA ENHANCED MRI IN PATIENTS UNDERGOING MAJOR HEPATECTOMY AFTER PVE

Is Function More Relevant than Volume?

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TRABALHO FINAL DO 6º ANO MÉDICO COM VISTA À ATRIBUIÇÃO DO GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DE MESTRADO INTEGRADO EM MEDICINA

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ABSTRACT

Introduction: Hepatic functional reserve assessment is crucial before major hepatectomy, particularly if portal vein embolization (PVE) is necessary, as these patients have greater risk of post-hepatectomy liver failure (PHLF). Since functional response to PVE occurs prior to future liver remnant (FLR) volumetric changes, Magnetic Resonance Imaging (MRI) with liver-specific contrast, particularly gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA), is a promising tool. Gd-EOB-DTPA enhanced MRI combines volumetric and signal intensity (SI) measurements, reflecting both liver anatomy and hepatocyte function. We intended to analyse the role of early Gd-EOB-DTPA enhanced MRI in preoperative assessment of hepatic functional reserve in high-risk patients undergoing PVE before major hepatectomy, comparing it to classic volumetric parameters.

Methods: Nine patients undergoing major hepatectomy after PVE (69.6±11 years; six men) were prospectively studied with Gd-EOB-DTPA enhanced MRI before and 10 days after PVE. We retrospectively selected eleven control patients who underwent the same procedures, studied only with volumetry (63±12 years; six men). We measured FLR volume, Degree of Hipertrophy (DH) and kinetic growth rate (KGR) for both groups. We also analysed embolised liver and FLR SI and relative liver enhancement (RLE) before and after PVE. Statistical significance with $p<0.05$.

Results: Volumetric-only parameters failed to correlate with post-hepatectomy liver function and morbidity. MRI parameters significantly correlated with pre- and post-operative levels of INR and albumin. FLR SI decreased after PVE in patients who developed PHLF ($p= 0.05$). Furthermore, after PVE, embolized liver RLE significantly dropped in patients who did not develop PHLF ($p=0.026$). In these patients, the difference between FLR and embolized liver RE significantly increased after PVE ($p=0.012$).

Conclusion: Gd-EOB-DTPA enhanced MRI can be used to define early hepatic functional response to PVE, predicting PHLF in cases that volumetric analysis fails to do so.

Keywords: Liver Neoplasms; Hepatectomy; Liver Function Tests; Magnetic Resonance; Liver Failure.

INTRODUCTION

Hepatic neoplasms are most often secondary locations of other malignant processes[1]. Colorectal cancer liver metastases (CRCLM) occur in more than 50% of patients with colorectal cancer, significantly hampering survival. Also, primary liver cancer, in particular hepatocellular carcinoma (HCC), is increasingly more prevalent, with risk factors including viruses with liver-specific tropism, alcoholic consumption and Nonalcoholic Steatohepatitis (NASH). NASH is directly related with rising rates of obesity, diabetes and metabolic syndrome[2,3], particularly in developed countries.

Both primary and secondary liver tumours rely on surgical resection as the only curative approach available[4–6]. In order to ensure tumour-free margins, surgeons often have to resect large volumes of hepatic parenchyma, with the risk of post-operative morbidity and mortality, in particular post-hepatectomy liver failure (PHLF). Classically, a future liver remnant (FLR) volume of less than 20% of the total liver volume (TLV) is associated with higher-risk of PHLF and other complications. This threshold increases to 30% in patients with non-cirrhotic liver disease and to 40% in compensated cirrhotic patients[7].

Percutaneous portal vein embolization (PVE), as first described in the English literature in 1986[8], has been widely used to enable surgical treatment in patients with insufficient FLR volume[7,9]. PVE excludes portal blood flow from the liver to resect, redirecting it to the FLR, causing an atrophy response of the tumour-containing hemiliver with compensatory hypertrophy of the contralateral parenchyma in the following weeks. With this minimally invasive technique, both volume and functional capacity of the FLR increase, minimizing the risk of complications, namely PHLF[7,9,10].

Volumetric response, usually measured with computed tomography, is the most used surrogate marker to evaluate liver functional response after PVE. However, volumetric change

might not be the most accurate indicator, as functional improvement may occur earlier and be more significant than mere volume increase[11].

Although the indocyanine green (ICG) clearance test is a widely-used liver-specific function test, it evaluates total liver function, limiting its use when liver function is not equally distributed across the parenchyma[12]. Liver scintigraphy with mebrofenin or galactosyl serum albumin marked with Technetium-99m (^{99m}Tc) can be used to evaluate total and partial liver function, useful when it comes to preoperative risk evaluation or post-PVE response assessment[13,14]. However, these tests usually lack in anatomic detail.

Gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA) is a liver-specific contrast agent used in MRI allowing volumetric and functional evaluation of the liver. Gd-EOB-DTPA enters the hepatocyte through the organic anion transporting polypeptides OATP1B1 and OATP1B3 and is excreted into the bile ducts unchanged via the multidrug resistance protein 2.[15,16] This paramagnetic contrast agent is a promising tool reflecting not only macro and microvasculature as well as hepatocyte uptake and excretion functions.

The main objective of this study is to compare liver volumetric and morpho-functional analysis in preoperative evaluation of high-risk patients undergoing major hepatectomy after PVE. For this, isolated hepatic volumetry will be compared to early functional and morphological evaluation of the liver with Gd-EOB-DTPA enhanced MRI. The primary endpoint will be the development of PHLF and mortality; the secondary endpoint will be pre- and post-hepatectomy liver function.

PATIENTS AND METHODS

This study was performed at Centro Hospitalar e Universitário de Coimbra, Portugal, and the patients included were identified using our institution's digital database.

To compare functional MRI to volumetry, we collected information of two independent groups of patients who underwent pre- and post-PVE evaluation with two different methods: MRI group and Volumetry group.

1. Study design

The MRI group patients were selected from an on-going prospective study. We included consecutive patients who underwent PVE at Serviço de Imagem Médica (Head of Department: Prof. Doutor Filipe Caseiro Alves) and subsequently underwent major hepatectomy for liver neoplasms at Serviço de Cirurgia III/A (Head of Department: Prof. Doutor Francisco Castro e Sousa [early period] and Prof. Doutor Júlio Soares Leite [currently]). These patients had pre- and early post-PVE morphological and functional evaluation with Gd-EOB-DTPA enhanced MRI between January 2014 and December 2017. Informed consent was obtained from all patients. This study was approved by the institution's Ethics Committee.

Patients in the Volumetry (control) group were identified from a retrospective database. Inclusion criteria included having completed PVE and major hepatectomy and having two complete volumetric studies (pre- and post-PVE evaluation). The patients' clinical characteristics were retrieved from the analysis of the individual clinical file, including information regarding the PVE procedure, peri-procedure and peri-operative laboratory results and pre- and post-embolization volumetric analysis. Patients included in the control group underwent major hepatectomy between July 2009 and September 2013.

Due to the decreased biliary elimination of Gd-EOB-DTPA in jaundiced patients, we excluded patients with perihilar cholangiocarcinoma in the prospective study, and thus also excluded any patient with this diagnosis in the Volumetry group.

2. Study population

According to our institution's policy, all cases were discussed in a multidisciplinary meeting. MRI and Volumetry groups are compared in Table 1.

2.1. MRI group

The MRI group included a total of nine patients (six men and three women). Mean age was 69.6 ± 11 years.

Six patients (66.7%) presented with hepatocellular carcinoma (HCC), all of them with a single nodule, median size of 62 mm (range 7-120 mm), with only one patient within the Milan criteria[17]. Five of the HCC (83.3%) developed in livers with hepatopathy: four with cirrhosis and one with NASH. Cirrhosis etiology included: hepatitis virus B, hepatitis virus C, alcohol consumption and one combining alcohol abuse and hepatitis virus C. Cirrhotic patients were staged as Child-Pugh[18] class A and had median Model for End-Stage Liver Disease (MELD)[19] score of 8 (range 6-11). All HCC patients underwent Transarterial Chemoembolization (TACE) before PVE. One patient had already undergone a minor liver resection due to HCC.

The remaining three patients in this group (33.3%) presented with colorectal cancer liver metastases (CRCLM), two metachronous (one of which had already undergone liver resection) and one synchronous presentation (Liver First approach). All CRCLM cases had unilateral location, with median 1 nodule (range 1-9) and median largest nodule size of 23 mm (range 22-43). Two patients received chemotherapy prior to PVE: one received 5 cycles of Folinic Acid + Fluouracil + Oxaliplatin (FOLFOX) and 3 cycles of cetuximab, with 8 weeks between

chemotherapy and surgical treatment; the other patient received 7 cycles of Folinic Acid + Fluouracil + Irinotecan (FOLFIRI), 4 cycles of cetuximab and 3 cycles of bevacizumab, with waiting period of 6 weeks between chemotherapy and surgery.

2.2. Volumetry group

Volumetry group included a total of eleven patients, six men and five women, mean age 62.7 ± 12.3 years.

Only two cases (18.2%) in the Volumetry group had HCC. One of these patients presented with a single 14 mm nodule in a liver with known chronic alcoholic hepatitis, having undergone TACE prior to PVE. The other patient presented with 3 nodules (largest nodule with 200 mm) implanted unilaterally in a liver with no documented liver disease.

The remaining nine patients (81.2%) in this group presented with liver metastases, eight being CRCLM and one gallbladder adenocarcinoma liver metastasis. Bilateral liver metastases were present in one case. Five cases (55.6%) had synchronous tumour presentation, two of which underwent synchronous resection. Median largest nodule size was 40 mm (range 19-95) with median 4 nodules (range 1-8).

Six patients in the Volumetry group received chemotherapy for liver metastases. The median total number of cycles was 13 (range 5-47). Three patients received FOLFIRI, one FOLFIRI and FOLFOX, one Capecitabine and Oxilaplatin and one other received different combinations of cytostatic agents (including Irinotecan, Fluorouracil and Oxaliplatin) with need of consecutive adjustments due to toxicity. The median period between chemotherapy and surgery in this group was 15 weeks (range 6-27).

Table 1. Study population consisting of nine patients (MRI group) undergoing early functional and volumetric study with Gd-EOB-DTPA enhanced MRI and eleven control patients (Volumetry group) having only volumetric assessment.

	MRI group (n=9)	**Volumetry group** (n=11)	**p value**
Sex (Male)	6 (66.7%)	6 (54.5%)	0.670
Age (years)	69.6 ± 11	62.7 ± 12.3	0.112
Diabetes mellitus	4 (44.4%)	4 (36.4%)	1.000
Right PVE	7 (77.8%)	8 (72.7%)	1.000
Hepatocellular carcinoma	6 (66.7%)	2 (18.2%)	0.065
Liver Metastases	3 (33.3%)	9 (81.8%)	
Number of nodules	1 (1-9)	3 (1-8)	**0.020**
Largest nodule diameter (mm)	50 (7-120)	40 (14-200)	0.824
Chronic Liver Disease	5 (55.6%)	1 (9.1%)	0.050
Cirrhosis	4 (44.4%)	0 (0%)	**0.026**
Previous chemotherapy	2 (22.2%)	6 (54.5%)	0.197
Number of cycles	6 (5-7)	13 (5-47)	0.381
Pre-operative MELD score	8 (6-11)	8 (6-10)	1.000
Previous hepatic resection	2 (22.2%)	2 (18.2%)	1.000

3. Portal vein embolization

PVE was successfully performed in all patients at first attempt. Both right and left PVE were performed through the right hemiliver. Laterality of PVE was comparable between groups (as shown in Table 1).

3.1. Embolization material

A combination of different embolic agents was frequently used to maximize vascular exclusion. The most frequently used agents were 0.035-inch coils, microspheres and Amplatzer^{TM} vascular plugs (St. Jude Medical, MN, USA).

Embolization material used is summarized in Table 2.

3.2. PVE-related morbidity and mortality

PVE-related mortality was 0% in our series.

Among the two groups, PVE-related morbidity occurred in one patient (5%) in the Volumetry group, with the development of portal vein thrombosis and cavernoma after PVE. However, this complication did not contraindicate resection.

Two patients (one from each group) underwent hepatic vein embolization due to insufficient hypertrophy after PVE.

Table 2. Embolic material used according to study group. MRI group – nine patients who underwent PVE between January 2014 and December 2017; Volumetry group – eleven patients who underwent PVE between July 2009 and September 2013.

	MRI group (n=9)	**Volumetry group** (n=11)	**p**
Coils + Microspheres	6 (66.7%)	3 (27.3%)	0.175
Amplatzer™ Plug	1 (11.1%)	4 (36.4%)	0.319
Amplatzer™ Plug + Microspheres + Coils	1 (11.1%)	2 (18.2%)	1.000
Amplatzer™ Plug + Microspheres	1 (11.1%)	1 (9.1%)	1.000
Coils + Cyanoacrilate	0 (0%)	1 (9.1%)	1.000

4. Gd-EOB-DTPA enhanced MRI

According to the approved prospective protocol applied in the MRI group, Gd-EOB-DTPA enhanced MRI was performed before and 10 days after PVE.

MRI exams were performed on Siemens® scanners, operating at 1.5-3T. Gd-EOB-DTPA (Primovist, Bayer Schering Pharma, Berlin, Germany) was administered at the recommended intravenous bolus dose of 0.1 mL/Kg, followed by a saline flush of 20 mL. T1 fat saturation sequences were performed before and after intravenous contrast administration in arterial (35s), portal (70s), transitional (180s) and hepatobiliary (20 minutes) phases of enhancement.

MRI analysis was performed by a radiologist blinded to patients' clinical data. The enhancement in both embolized liver and FLR, as well as the spleen, was measured in pre-contrast and hepatobiliary phases. Signal intensity (SI) was acquired by placing predefined regions of interest (ROIs) in such areas, excluding important vessels and tumour lesions.

Liver enhancement ratio (LER), calculated for both pre-contrast and hepatobiliary phases, was defined as follows:

$$\text{LER} = \frac{Liver\ signal\ intensity}{Spleen\ signal\ intensity}$$

Relative Liver enhancement (RLE) was defined as the difference between LER in hepatobiliary (LERhb) and pre-contrast (LERp) phases:

$$\text{RLE} = LERhb - LERp$$

LER and RLE were calculated for both FLR and embolized liver. The difference between FLR and embolized liver RLE was calculated for both sets of images.

5. <u>FLR volumetric response after PVE</u>

Volumetric analysis was performed by a radiologist blinded for clinical data, based on imaging using validated Osirix® software (Pixmeo, Geneva, Switzerland).

Pre- and post-embolization FLR volumes were calculated for both groups of patients. In the MRI group, pre- and post- PVE Gd-EOB-DTPA enhanced MRI exams were assessed. In the Volumetry group, pre- and pos-t PVE imaging studies, either CT (performed in 64-slice scanner GE®) or MR (performed Siemens® scanners, operating at 1.5-3T) were assessed.

We also measured pre-embolization Total Liver Volume (TLV) and calculated pre- and post-PVE FLR volume percentage:

$$\text{Pre-PVE FLR (\%)} = \frac{pre{-}PVE\ FLR\ volume}{TLV} * 100$$

$$\text{Post-PVE FLR (\%)} = \frac{post{-}PVE\ FLR\ volume}{TLV} * 100$$

Degree of Hypertrophy (DH) and Kinetic Growth Rate (KGR) were defined as follows:

$$\text{DH (\%)} = \text{Post-PVE FLR (\%)} - \text{Pre-PVE FLR (\%)}$$

$$\text{KGR} = \frac{DH\ (\%)}{number\ of\ weeks\ between\ assessments}$$

6. Surgical procedures

Waiting period between PVE and surgery slightly differed between groups, although this difference did not reach statistical significance. Median number of days between embolization and resection was 38 (14-261) in the MRI group and 50 (18-733) days in the Volumetry group (p=0.370) (Table 3).

In all but one case (laparoscopic right hepatectomy), liver resection was performed through open approach, through a bilateral subcostal incision. Our department's technique has been previously described[20].

After ruling out unexpected disseminated disease, the liver is mobilized and intraoperative ultrasound is routinely performed. Parenchymal transection is either performed with CUSA™ Ultrasonic Surgical Aspirator or Kelly-clamp crush technique. Careful revision of hemostasis and biliostasis is done before abdominal closure.

When possible, resection is performed with selective vascular exclusion of only the parenchyma to remove. Intermittent pedicle clamping (IPC) (15 minutes clamping with 5 minutes reperfusion; 10 minutes clamping in the case of chronic liver disease, as previously reported[12]) and total vascular exclusion (TVE) are only applied when deemed necessary. IPC was employed in 14 (70%) of the 20 patients in this study, median 3 clamping periods (range 1-5) for a cumulative time of 30.5 minutes (range 12-76). TVE was necessary in one patient (5%) for a total period of 20 minutes.

Twelve patients (60%) required intra-operative red blood cells transfusion (RBC), median 600 mL (range 300-3600 mL). Also 60% of patients received fresh frozen plasma (FFP) intra-operatively, median 400 units (range 200-2000 mL).

Overall, 15 patients (75%) underwent Right Hepatectomy: eight formal (40%), four extended (20%) and three associating atypical left liver resections (15%). The remaining 5 patients in our series (25%) underwent left hepatic resections: three (15%) formal left hepatectomies, one (5%) extended left hepatectomy and one left lobectomy (10%), in a patient who had previously undergone segments 5, 6 and 7 resection, therefore not being excluded of this study. Laterality of the diseased liver did not differ among the two study groups in this study, as shown in Table 1.

MRI and Volumetry groups did not significantly differ in any intra-operative parameter (Table 3).

7. Post-operative course

Post-operative morbidity and mortality were registered within 90-days after resection. Surgical complications were evaluated as defined by Dindo-Clavien[21]. PHLF was defined both by the "50-50 criteria"[22] and the International Study Group of Liver Surgery (ISGLS) criteria[23]. Posthepatectomy haemorrhage[24] and bile leakage[25] were also defined according to ISGLS criteria.

Mortality occurred in one patient in each group (overall mortality 10%). In the Volumetry group a patient suffered intraoperative cardiac arrest, while in the MRI group one patient died on post-operative day 14, due to grade C PHLF with multiorgan dysfunction.

Surgical complications occurred in 13 (65%) of the 20 patients in this study, ten (50%) corresponding to major morbidity (Dindo-Clavien III and higher).

Post-hepatectomy haemorrhage and bile leakage occurred in two (10%) and six (30%) patients respectively.

The 50-50 criteria were not fulfilled by any patient in this series. Nevertheless, PHLF according to ISGLS criteria occurred in 6 patients (30%) – four (20%) Grade A, one (5%) Grade B and one (5%) Grade C.

Study groups had statistically comparable postoperative outcomes (Table 3).

Table 3. Comparison of intra-operative data and post-operative morbidity and mortality according to study group. All patients underwent major hepatectomy after PVE, nine of which (MRI group) having been studied with Gd-EOB-DTPA enhanced MRI before and after the procedure.

	MRI group (n=9)	**Volumetry group** (n=11)	**p value**
No. of days from PVE to resection	38 (14-261)	50 (18-733)	0.370
Hepatic Pedicle Clamping	6 (66.7%)	8 (72.7%)	0.574
Cumulative time (min.)	29.5 (12-43)	46 (15-76)	0.228
No. of Clamping periods	2 (1-4)	4 (1-5)	0.108
RBC transfusion	4 (44.4%)	8 (72.7%)	0.205
Volume (mL)	750 (300-1200)	450 (300-1800)	0.683
FFP transfusion	4 (44.4%)	8 (72.7%)	0.205
Volume (mL)	400 (400-400)	500 (200-2000)	0.368
Mortality	1 (11.1%)	1 (9.1%)	1.000
Morbidity	6 (66.7%)	7 (63.6%)	1.000
Clavien I-II	2 (22.2%)	1 (9.1%)	
Clavien III-V	4 (44.4%)	6 (54.5%)	
PHLF ISGLS	4 (44.4%)	2 (18.2%)	0.350
Grade A	3 (33.3%)	1 (9.1%)	
Grade B	0 (0%)	1 (9.1%)	
Grade C	1 (11.1%)	0 (0%)	
Post-hepatectomy haemorrhage	1 (11.1%)	1 (9.1%)	1.000
Grade A	1 (11.1%)	0 (0%)	
Grade B	0 (0%)	1 (9.1%)	
Bile Leakage	2 (22.2%)	4 (36.4%)	0.642
Grade A	0 (0%)	1 (9.1%)	
Grade B	2 (22.2%)	3 (27.3%)	

8. Pathologic information

Information on both tumoural and non-tumoural liver parenchyma was reviewed using pathology reports.

Tumour-free margins (R0) were achieved in 16 patients (80%), while four patients had microscopically infiltered margins (R1).

A normal non-tumoural parenchyma was found in only three patients (15%). Fibrosis was evident in eight (40%) cases while only one (5%) patient presented with histological cirrhosis. Sinusoidal obstruction syndrome was diagnosed in three patients (15%), while other two (10%) presented with sinusoidal dilation and mild nodular regeneration.

In one case non-tumoural parenchyma information was not included in the pathology report.

Weight of resected parenchyma did not differ between groups.

Table 4. Pathologic information obtained through revision of pathology reports. MRI group includes nine patients who underwent major hepatectomy, six with HCC and three with CRCLM. Volumetry group includes 11 cases, nine liver metastases and two HCC.

	MRI group (n=9)	**Volumetry group** (n=11)	**p value**
Resection margins			
R0	8 (88.9%)	8 (72.7%)	0.591
R1	1 (11.1%)	3 (27.3%)	
Non-tumoural parenchyma			
Normal	0 (0%)	3 (27.3%)	0.211
Mild Steatosis	0 (0%)	2 (18.2%)	0.474
Sinusoidal dilation	0 (0%)	1 (9.1%)	1.000
Sinusoidal Obstruction Syndrome	2 (22.2%)	1 (9.1%)	0.582
Nodular Regeneration	1 (11.1%)	0 (0%)	0.474
Fibrosis	5 (55.6%)	3 (27.3%)	0.370
Cirrhosis	1 (11.1%)	0 (0%)	0.474
No information	0 (0%)	1 (9.1%)	1.000
Resected Weight (g)	525 (292-1600)	500 (215-3800)	0.710

9. Statistical analysis

Statistical analysis was performed using SPSS^{TM} software version 22.0. Quantitative data were expressed by mean ± standard deviation and compared using Student's t-tests and Mann-Whitney U test as fitting. Categorical variables were expressed by absolute and relative frequencies and compared using Chi-square test. Correlation of continuous variables was performed with Pearson correlation. Statistical significance was defined by $p<0.05$.

RESULTS

1. Volumetric response to PVE

Considering the whole population, when comparing pre- and post-embolization sets of images, FLR volume significantly increased between assessments (35.1±14.3 and 41.9±15.6 – $p<0.001$).

Overall, FLR hypertrophy parameters did not differ between groups. As expected from the study methodology, the number of days between PVE and post-PVE imaging assessment (Gd-EOB-DTPA enhanced MRI or volumetric assessment) significantly differed between study groups (p=0.016), as patients in the MRI group were all evaluated 10 days after PVE, much earlier than the Volumetry group.

Table 5 – FLR volumetric response after PVE compared according to study groups. MRI group includes nine patients evaluated before and 10 days after PVE with Gd-EOB-DTPA enhanced MRI. Volumetry group includes eleven patients reviewed retrospectively with pre- and post-PVE volumetric assessment.

	MRI group (n=9)	**Volumetry group** (n=11)	**p value**
Days between PVE and re-assessment	10±0.0	21.2±12.6	**0.016**
Pre-PVE FLR (%)	31.8±10	38.8±16.6	0.412
Post-PVE FLR (%)	35.9±9.6	46.2±17.9	0.238
Degree of Hypertrophy (%)	5.8±4.1	7.5±7.5	0.778
KGR (%/week)	4.1±2.9	2.7±2.5	0.492

2. Volumetric response and surgical outcomes

When considering the whole study population (n=20), volumetric parameters were not able to predict post-operative surgical morbidity or PHLF, with statistically similar distributions among groups of patients who did and did not develop such complications. In what comes to 90-day mortality, some volumetric parameters did differ between groups, as shown in Table 6.

Since number of days elapsed between PVE and post-PVE assessment significantly differed between groups (p=0.016 – Table 5), we proceeded to analyse volumetric parameters' influence on post-operative morbidity and mortality separately for each of the defined study groups.

When analysing FLR volume comparing pre- and post-PVE values with paired samples student's t-test, there was a significant increase both in patients who did and did not develop PHLF (p=0.002 and p=0.05 respectively).

However, both in MRI and Volumetry groups, volumetric parameters failed to correlate in a statistically significant way with any of the established surgical outcomes. Table 6 contains detailed information on Volumetric parameters distribution according to study groups and surgical outcomes.

Table 6 – Comparison of distribution of volumetric parameters according to 90-day mortality, major morbidity (Dindo-Clavien III or higher) and PHLF (ISGLS criteria), considering the whole study population (n=20), MRI group (n=9) and Volumetry group (n=11). MRI group underwent Gd-EOB-DTPA enhanced MRI before and 10 days after PVE. Volumetry group variables were obtained through retrospective review of images acquired before and 21.2±12.6 days after PVE.

	Total population			**MRI group (n=9)**			**Volumetry group (n=11)**		
Mortality	**Yes (n=2)**	**No (n=18)**	**p value**	**Yes (n=1)**	**No (n=8)**	**p value**	**Yes (n=1)**	**No (n=10)**	**p value**
Pre-PVE FLR volume (%)	20.9±0.74	37.3±13.9	**0.042**	20.3	33.2±9.7	0.222	21.4	40.5±16.4	0.364
Post-PVE FLR volume (%)	22.7±1.2	44.1±14.8	**0.023**	21.8	37.9±8.3	0.250	23.6	48.5±17.1	0.364
Degree of Hypertrophy (%)	1.8±0.5	7.4±6.3	**0.047**	1.48	6.4±4.0	0.250	2.2	8.0±7.7	0.364
KGR (%/week)	0.7±0.5	3.6±2.7	0.070	1.04	4.5±2.8	0.250	0.37	2.9±2.5	0.364
Major morbidity	**Yes (n=10)**	**No (n=10)**	**p value**	**Yes (n=4)**	**No (n=5)**	**p value**	**Yes (n=6)**	**No (n=5)**	**p value**
Pre-PVE FLR volume (%)	31.8±8.3	39.5±17.9	0.436	26.8±5.0	35.8±11.7	0.286	35.0±8.7	43.2±23.4	0.662
Post-PVE FLR volume (%)	39.5±14.6	44.5±16.9	0.549	31.1±7.5	40.6±9.8	0.343	45.1±16.9	47.7±21.8	0.931
Degree of Hypertrophy (%)	7.7±7.6	5.7±4.5	0.905	4.3±2.8	7.3±5.0	0.343	10.0±9.1	4.43±4.1	0.537
KGR (%/week)	2.9±2.1	3.7±3.3	0.447	3.0±2.0	5.1±3.5	0.343	2.8±2.3	2.5±3.01	0.931
Post-hepatectomy Liver Failure	**Yes (n=6)**	**No (n=14)**	**p value**	**Yes (n=4)**	**No (n=5)**	**p value**	**Yes (n=2)**	**No (n=9)**	**p value**
Pre-PVE FLR volume (%)	30.8±10.2	37.7±15.4	0.239	29.6±11.1	33.6±9.9	0.190	33.3±11.2	40.0±17.8	0.727
Post-PVE FLR volume (%)	33.3±11.7	44.9±15.9	0.130	28.6±6.9	40.2±8.5	0.071	40.3±16.9	47.6±18.8	0.909
Degree of Hypertrophy (%)	5.5±4.4	7.3±6.9	0.622	4.4±4.3	6.7±4.2	0.393	7.1±5.6	7.6±8.1	1.000
KGR (%/week)	2.7±2.2	3.5±2.9	0.559	3.1±3.0	4.7±2.9	0.393	2.1±0.4	2.8±2.8	0.727

3. Gd-EOB-DTPA enhanced MRI and pre-operative liver function

Before PVE, FLR parenchyma SI in hepatobiliary phase had significantly negative correlations with pre-embolization (Pearson r=-0.854; p=0.007) and pre-operative values of International Normalized Ratio (INR) (Pearson r=-0.737; p=0.023). FLR parenchyma SI in hepatobiliary phase continues to negatively correlate with pre-operative INR after PVE (Pearson r=-0.807; p=0.015).

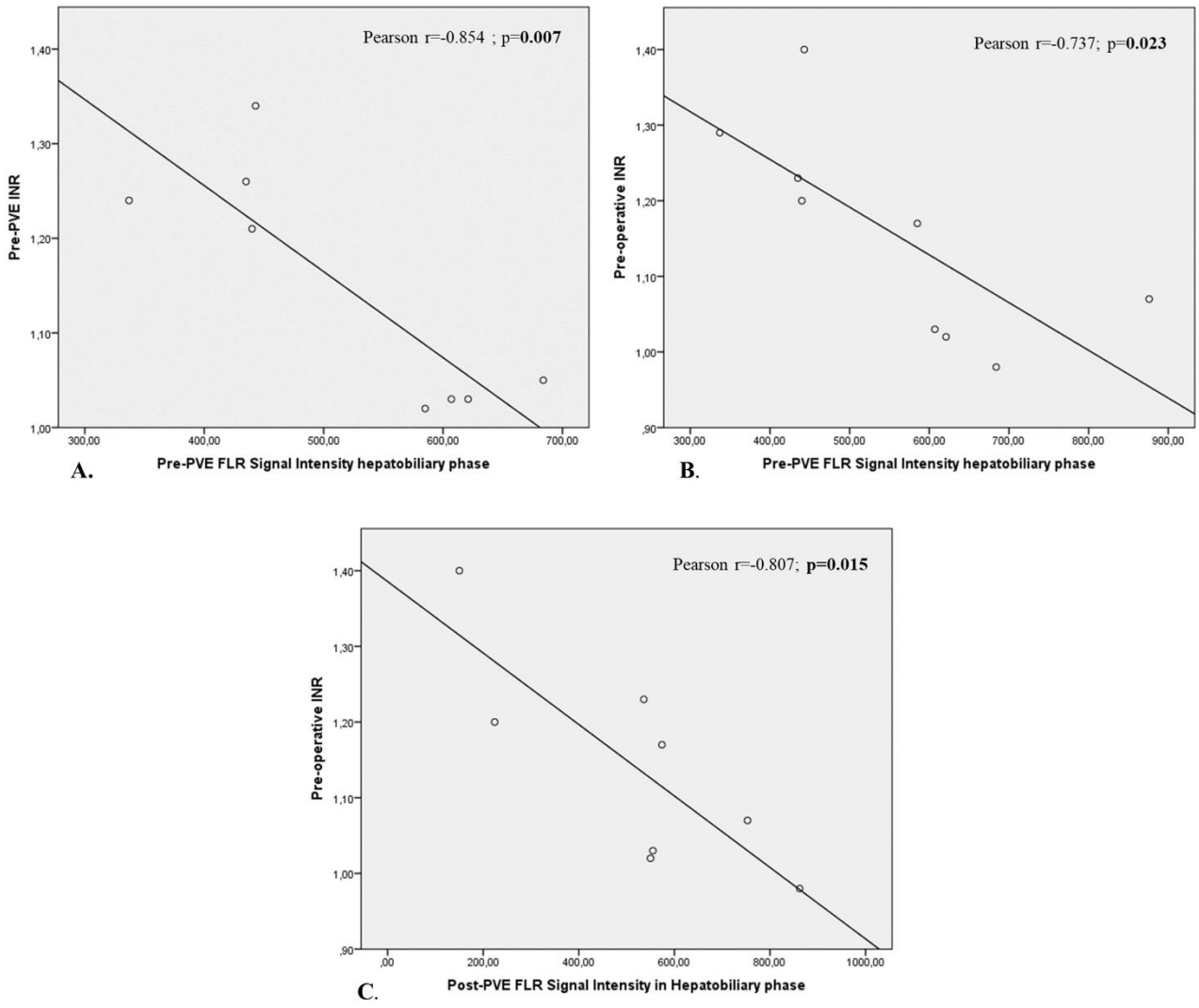

Figure 1. – Correlation between FLR Signal Intensity in Hepatobiliary phase before and after PVE and INR values. GD-EOB-DTPA enhanced MRI was obtained pre- and 10 days post-PVE in the MRI group. **A. -** Correlation between pre-PVE FLR SI and INR value. **B.-** Correlation between pre-PVE FLR SI and preoperative INR. **C. –** Correlation between post-PVE FLR SI and pre-operative INR.

The increment in the difference between FLR and embolized liver RLE strongly correlated with pre-operative levels of albumin in our series of patients (Pearson r=0.869; p=0.005). – Figure 2.

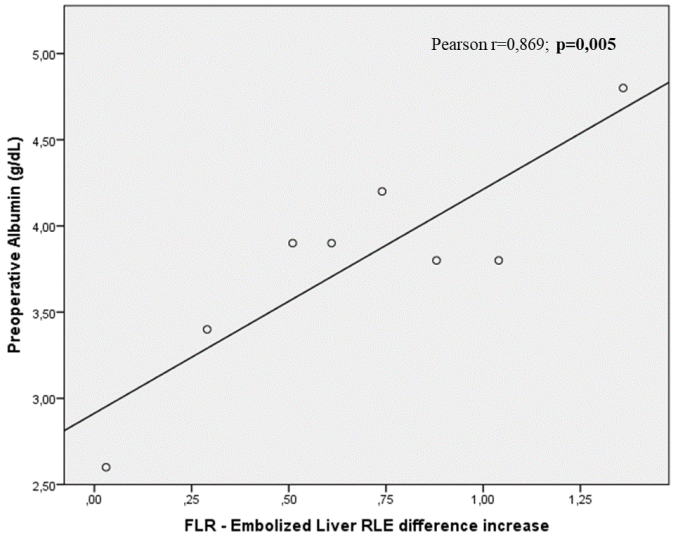

Figure 2. – Correlation between FLR and embolized liver RLE difference increase and pre-operative value of serum albumin(g/dL) in patients who underwent Gd-EOB-DTPA enhanced MRI before and 10 days after PVE.

4. Gd-EOB-DTPA enhanced MRI and post-operative liver function

FLR SI in hepatobiliary phase negatively correlated with post-operative day 3 INR value (Pearson r=-0.753; p=0.031). – Figure 3.

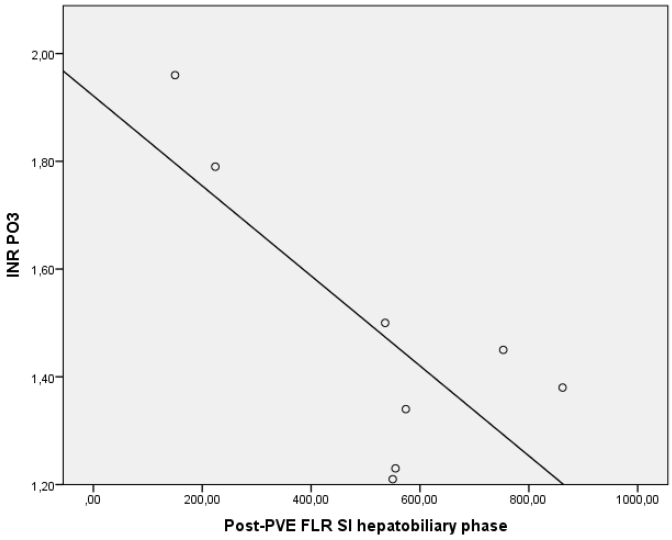

Figure 3. – Significant correlation between Post-PVE FLR SI (obtained 10 days after the procedure) and INR value on post-operative day 3.

5. Gd-EOB-DTPA enhanced MRI parameters response to PVE

We were not able to define any significant change in MRI parameters as predictive of mortality.

Considering FLR SI in hepatobiliary phase, pre-PVE exams displayed a mean value of 586.4±151.2 suffering no statistically significant alterations when compared with post-PVE values of 525.5±239.3 (p=0.303). Patients who did not develop PHLF did not have their FLR SI significantly altered either (p=0.576). Nevertheless, for those patients in the MRI group who did suffer PHLF, FLR SI interestingly dropped after PVE (p=0.05) – Figure 4.

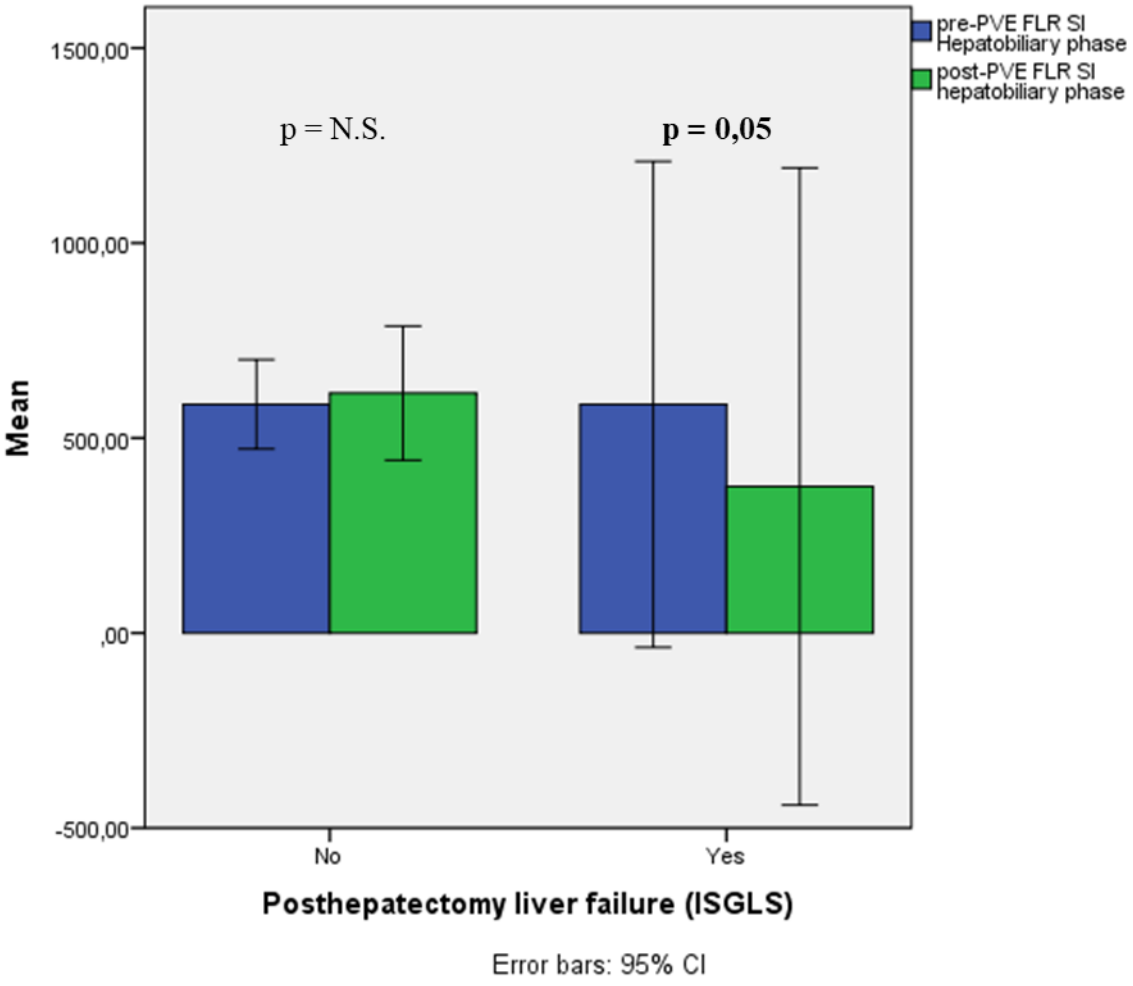

Figure 4. - FLR SI in hepatobiliary phase before and after PVE, according to the development of PHLF. Patients without PHLF had no statistically significant improvement of FLR SI (586.4±92.3 and 615.4±138.5 – p=0.576). Patients with PHLF had FLR SI decreased after PVE (586.3±250.9 and 375.7±328.9 – p=0.05).

Embolized liver RLE had pre-PVE values of 1.2±0.65, significantly dropping to post-PVE values of 0.65±0.53 (p=0.007). When compared according to the development of PHLF, embolized liver RLE significantly dropped in patients who did not develop PHLF (p=0.026). On the other hand, when considering patients who had compromised liver function post-operatively, embolized liver RLE did not display any significant alteration between functional MRI assessments (p=0.243) – Figure 5.

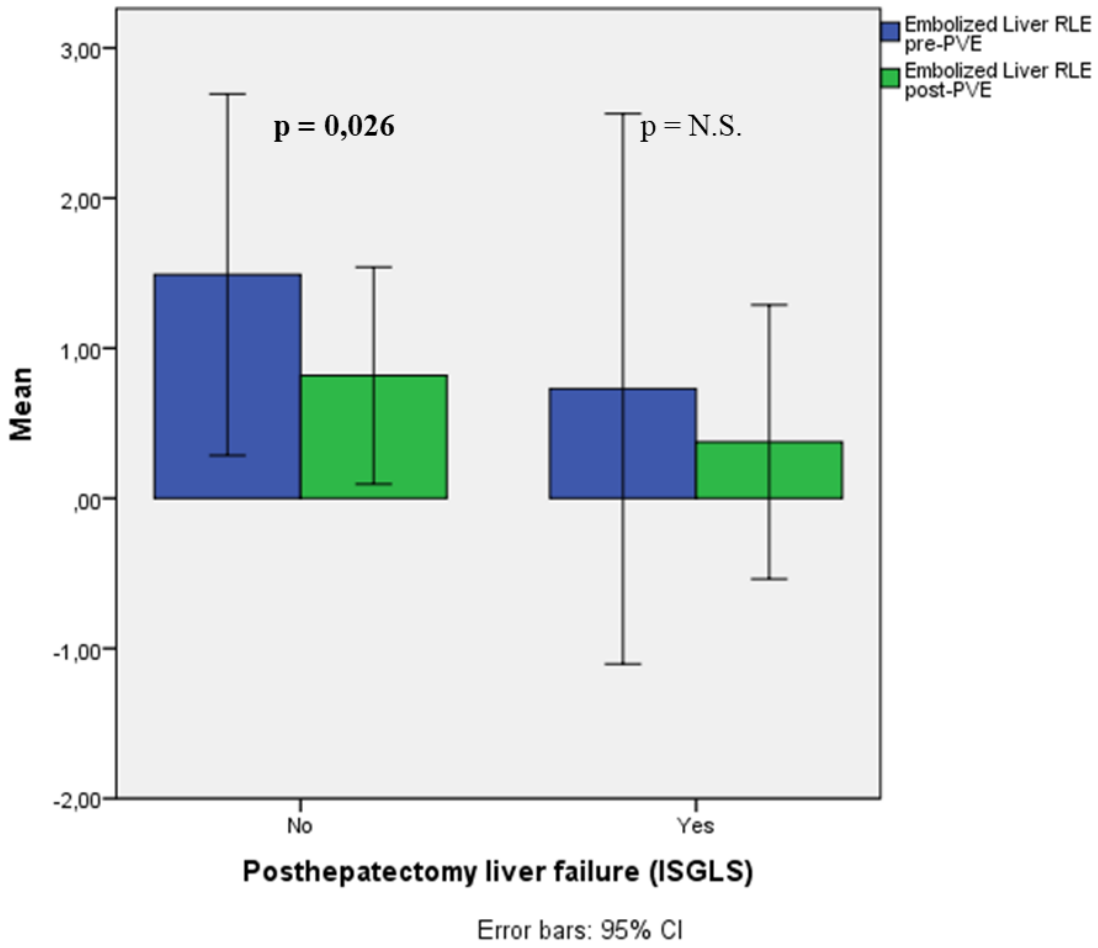

Figure 5. - Embolized liver RLE before and after PVE, according to the development of PHLF. Patients without PHLF had statistically significant decrease of embolized liver RLE (1.5±1.0 and 0.8±0.6 – p=0.026). Patients with PHLF displayed no significant change in embolized liver RLE (0.7±0.7 and 0.4±0.4 – p=0.243).

In the MRI group, for each set of images we calculated the difference between FLR and embolized liver RLE (ΔRLE). Before PVE, ΔRLE had a mean value of -0.11±0.41, increasing to 0.57±0.25 after PVE, when considering the whole group (p=0.003).

As shown in Figure 4, ΔRLE showed a significant increment between pre- and post-PVE MRI assessments in patients who did not develop PHLF according to ISGLS criteria (p=0.012). When considering patients with post-hepatectomy compromise of liver function, this difference did not demonstrate any significant change (p=0.214) – Figure 6.

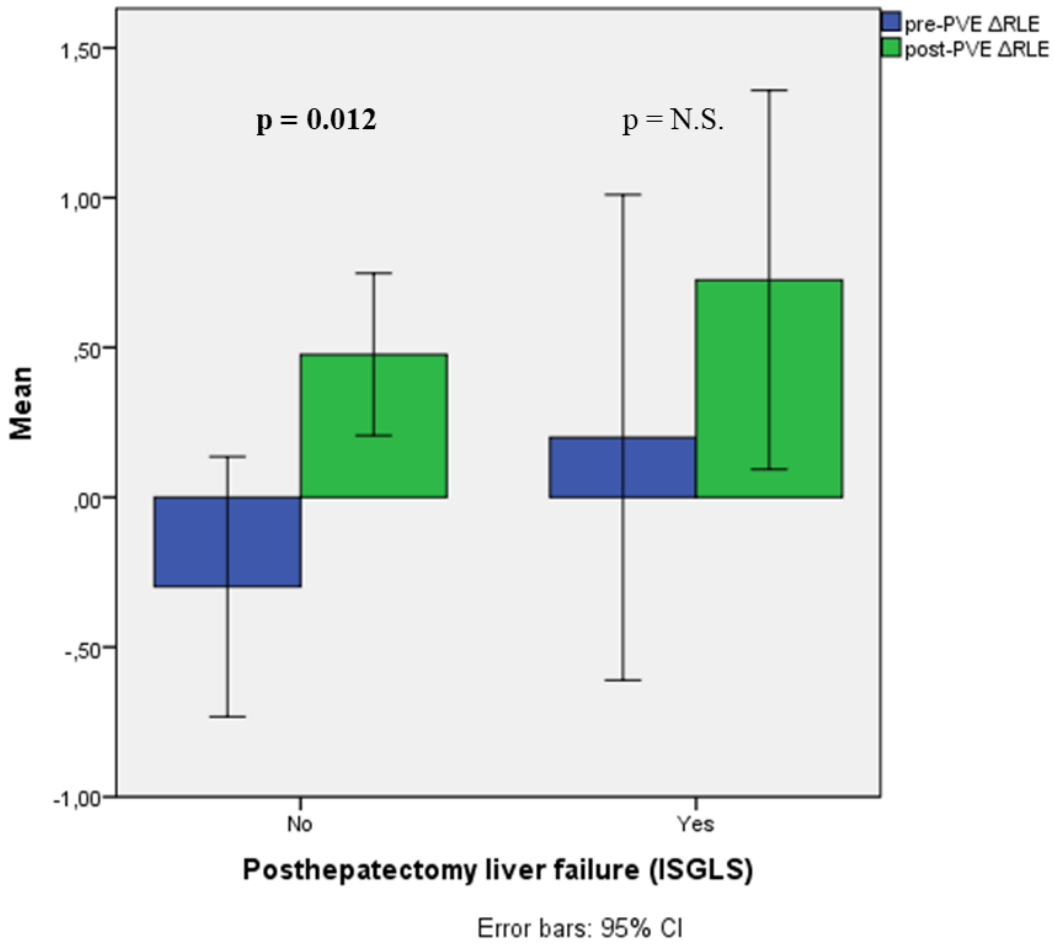

Figure 6. – Difference between FLR and embolized liver RLE (ΔRLE) before and after PVE, according to the development of PHLF. Patients without PHLF had statistically significant increase of ΔRLE (-0.3±0.3 and 0.5±0.2 – p=0.012). Patients with PHLF displayed no significant change in this parameter (0.2±0.3 and 0.7±0.3 – p=0.214).

Illustrating one of the most significant findings in the present work, we present the comparison between pre- and post-embolization Gd-EOB-DTPA enhanced MRI images of two patients (Figure 7): one without any postoperative impairment in liver function; and one patient with grade C PHLF. Embolized liver decrease in signal intensity and difference between FLR and embolized liver RLE are notorious in Patient 1, particularly in image B.

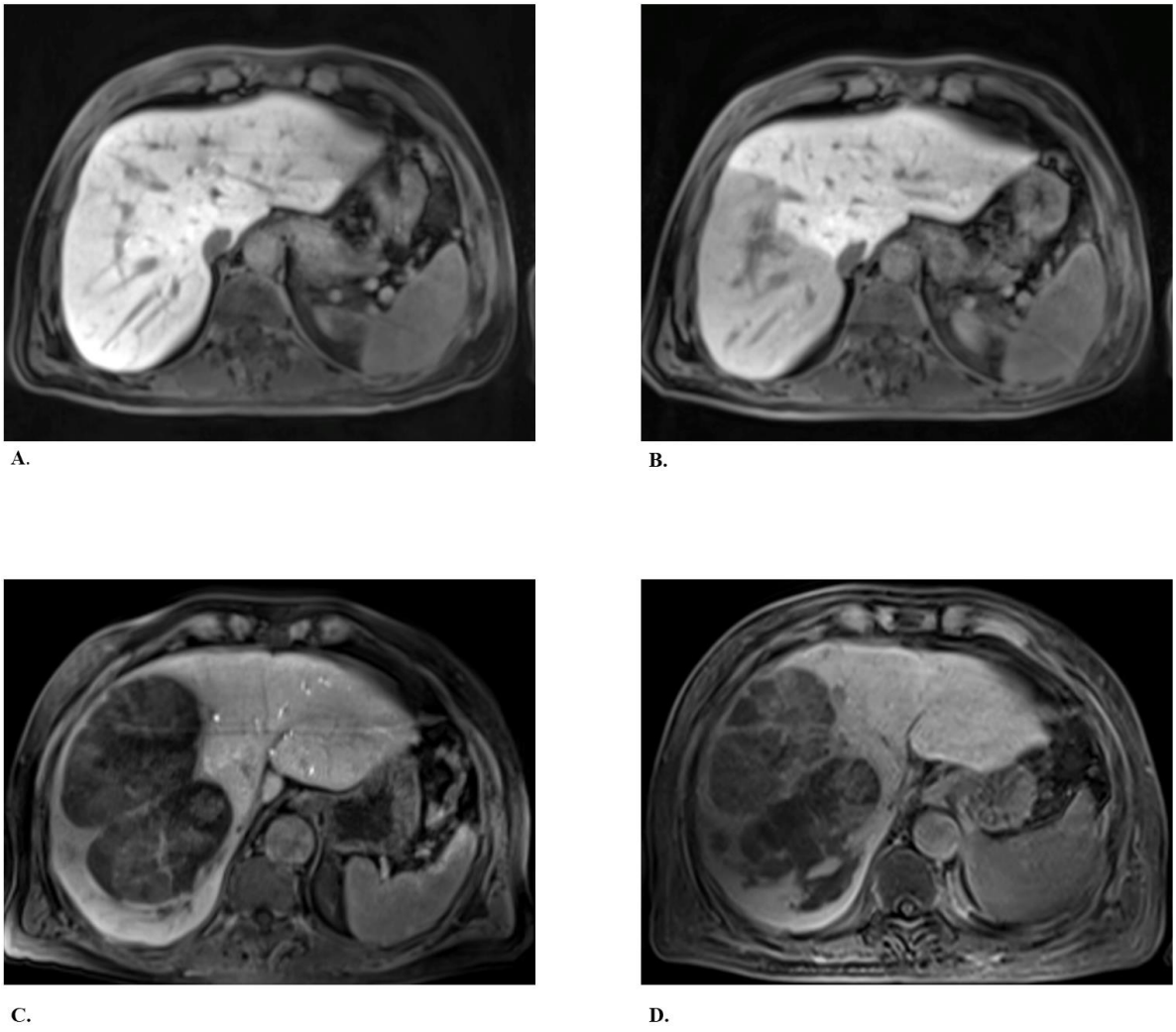

Figure 7. Pre- and 10 days post right PVE Gd-EOB-DTPA enhanced MRI images of two patients in the MRI group. Patient 1 (images A and B), male, 78 years old, single HCC nodule with 50 mm largest diameter, did not suffer any post-operative impairment of the liver function after right hepatectomy. Patient 2 (imagens C and D), male, 75 years old, single HCC nodule with 120mm largest diameter, suffered Grade C PHLF with associated mortality 14 days after resection.

DISCUSSION

Although PVE has been used to widen the pool of patients with liver neoplasms that are amenable to liver resection, the best way to evaluate preoperative liver function reserve remains an issue of discussion. Isolated volumetric parameters have been progressively questioned as accurate markers of functional reserve, since volumetric and functional response of the liver might not be simultaneous.

The ALPPS procedure (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy), although increasingly popular among hepatobiliary surgeons, remains hampered by high postoperative mortality, usually due to PHLF. In these patients, size of FLR has been questioned as an adequate predictor of morbidity and mortality.[26] Also in the setting of PVE, static volumetry alone is less sensitive than more dynamic growth variables, such as the Kinetic Growth Rate[27].

This was confirmed in our series. In fact, we report a measurable and significant difference in volumetric parameters after PVE assessments and surprisingly this occurred in the MRI group as early as 10 days after PVE. However, this increase failed to correlate with post-operative outcomes, namely PHLF, since both patients who did and did not show compromised post-hepatectomy liver function had similarly significant increases in their FLR volume.

Atrophy-hypertrophy events that occur after PVE and ALPPS stage 1 have been related with significant functional improvements that might not be directly related with volumetric response grade. Early functional evaluation after these procedures is of the utmost importance since tumour progression might occur in the waiting period to major resection. Although hepatobiliary scintigraphy has been presented as a candidate method to early functional assessment after ALPPS stage 1[28], this technique lacks anatomical detail, being useless to define the existence of tumour progression that might contra-indicate resection.

Gd-EOB-DTPA enhanced MRI presents as a high definition morphological and functional liver study. Early in the arterial and venous phases, Gd-EOB-DTPA acts like a non-specific agent, defining liver vasculature allowing volumetric analysis and helping in liver tumour characterization. Regional liver functional assessment can also be achieved with this technique through the definition of different ROIs in the hepatobiliary phase, when hepatocyte uptake occurs. Impaired liver function will be reflected as decreased enhancement and prolonged enhancement time in such regions[16].

Despite the small size of the MRI group, an interesting relation of MRI parameters was observed with the INR value both pre- and post-operatively. INR is widely used as part of hepatic disfunction grading scores[18,19], being a non-specific marker of liver synthesis of clothing factors. Preoperative serum albumin, another hepatic-synthetized protein and a key component of the Child-Pugh score, was also correlated with functional MRI parameters. These correlations reinforce the role of this method in the evaluation of liver function.

Although we did not find any association with postoperative mortality, in our study, Gd-EOB-DTPA enhanced MRI parameters showed higher capacity in predicting post-operative liver dysfunction than classical volumetric parameters. Although previous studies corroborate MRI utility in pre-operative liver function monitoring[29,30], we point out to the precocity of post-PVE assessment (10 days), when compared with other similar studies. This seems to confirm the thesis that the functional response to PVE might be detectable in a very early stage.

Early embolized liver response to PVE surfaced as a very interesting discriminative parameter between patients who did and did not suffer PHLF. This finding, consequence of the deviation of portal blood flow to the non-embolized liver, surely reflects a pronounced and progressive loss of function in the embolized liver.

Although the FLR failed to demonstrate an expected increment of the SI in hepatobiliary phase after PVE in patients with good post-operatory function, this parameter suffered a

decrease in patients with post-operative liver function impairment. This finding might translate a poor accommodating capacity of the FLR to the portal hyperflux after PVE. In a liver with a poor regenerating capacity, portal overflow might compromise liver function, reflected in our series as a decrease in SI after PVE and a post-operative inability to cope with the surgical liver injury. Since SI values alone might not be the best parameters when comparing two sets of MRI images, we are aware that these results must be analysed with caution.

Accordingly, the most significant finding of our study was the fact that when considering ΔRLE changes after PVE, Gd-EOB-DTPA enhanced MRI was an accurate predictor of PHLF. Patients without this complication presented a consistent post-PVE increase in ΔRLE, while patients suffering from PHLF had no significant change. In biological terms, this response in ΔRLE reflects the reciprocal change of function between hemilivers, secondary to the changes in portal flow, from the embolized to the non-embolized hemiliver.

The role of embolized liver response and difference between FLR and embolized liver are extremely interesting parameters to be further investigated in larger series.

However, we also recognize some weaknesses of the present study that warrant caution in the interpretation of the results. Firstly, although Gd-EOB-DTPA enhanced MRI studies were obtained with a prospective protocol, control group patients were retrospectively selected. Secondly, even though study groups were fairly similar in most clinical parameters, indication for surgery was clearly different between groups. This closely correlates with the fact that MRI group patients are the most recently treated in this study. In recent years, patients presenting with bilobar diffuse metastatic disease are more likely to undergo staged hepatectomy, including the ALPPS procedure, considering tumour progression risk after PVE. On the other hand, patients presenting with HCC are increasingly accepted for surgical treatment once safety criteria are fulfilled (adequate hepatic function assessed with ICG clearance test and exclusion of portal hypertension). Furthermore, the number of patients in each group is limited, requiring

further confirmation with larger prospective groups. Lastly, we did not investigate this method in a particular subset of patients with high risk of PHLF, namely patients undergoing extended hepatectomy for perihilar cholangiocarcinoma.

Early morphological and functional MRI with Gd-EOB-DTPA presents as a promising manner of identifying patients in risk of PHLF, diminishing the waiting period between PVE and resection and controlling tumour progression risk. Specific cut-off values for MRI parameters must be investigated in order to maximize MRI utility in clinical practice. This PHLF risk measurement has significant clinical implications after PVE, as other techniques might be necessary to ensure resection safety. Hepatic vein embolization and rescue-ALPPS[31] are possible approaches once PVE proves insufficient in incrementing liver functional reserve.

Also, this method seems to be particularly suited for the interstages assessment of function in the ALPPS procedure, given the need for a very accurate anatomic detail of FLR function. Our group is presently conducting a study in this context.

Finally, other potential uses for MRI in the preoperative setting include the assessment of liver parenchyma diseases, investigation of ischemia-reperfusion injury and evaluation of liver energetic capacity. Multiparametric MRI might be an useful tool for physicians to define liver inflammation and fibrosis grading, presenting as a promising non-invasive future substitute of liver biopsy[29]. Diffusion-weighted MRI and liver-specific contrast enhanced MRI can be used to study ischemia-reperfusion liver injury, an important insult to liver function after partial hepatectomy and potentially after PVE and ALPPS stage 1[32]. Also, MRI with liver-specific contrast, can also be useful in sinusoidal obstruction syndrome diagnosis of chemotherapy-treated patients[33], a frequent situation in patients undergoing major hepatectomy for CRCLM. Finally, liver energetic adaptations, extremely important in liver regeneration after hepatectomy[34] can also be assessed with magnetic resonance studies, particularly magnetic resonance spectroscopy using 31-Phosphorous[35]. All these potential applications of MRI

techniques bring them to the spotlight as the future of preoperative liver morphological and functional evaluation.

CONCLUSION

MRI techniques, in particular early GD-EOB-DTPA enhanced MRI, are of enormous potential value in pre-operative assessment of patients undergoing major hepatectomy for liver neoplasms after PVE. Early functional assessment played a discriminating role between patients who did and did not develop PHLF, while volumetric assessment failed to do so. In the near future, MRI will surely contribute to a more precise and safe estimation of pre-operative liver function, particularly after PVE or between ALPPS stages, thus decreasing the risk of morbidity and mortality.

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1. **Apresentação oral:** "Ressonância Magnética com Contraste Hepato-Específico: Um Método Sensível para a Avaliação e Visualização da Reserva Hepatocelular Pré-Hepatectomia?" – Congresso Português de Hepatologia 2016, uma iniciativa da Associação Portuguesa para o Estudo do Fígado (APEF).

Henrique Alexandrino, Henrique Donato, Mariana Duque, Luís Ferreira, Ricardo Martins, Marco Serôdio, Mónica Martins, Alfredo Gil Agostinho, Paulo Donato, José Guilherme Tralhão, Filipe Caseiro Alves, Francisco Castro e Sousa

2. **Apresentação oral**: "Early Volumetric and Functional Imaging Assessment of Portal Vein Embolisation" – apresentado no Congresso Mundial da CIRSE - Cardiovascular and Interventional Radiological Society of Europe em Setembro de 2017.

H. Donato, H. Alexandrino, M. Duque, P. Belo Oliveira, P. Donato, A. G. Agostinho, F. Caseiro-Alves

3. **Apresentação oral**: "Early Functional Response after Portal Vein Embolization – Difference between Future Liver Remnant and Embolized Liver Relative Enhancement as a Marker of Improved Hepatocellular Reserve" - submetida para o 13th IHPBA (International Hepato-Pancreato-Biliary Association) World Congress.

Mariana Duque, Henrique Alexandrino, Henrique Donato, Ricardo Martins, Marco Serôdio, José Guilherme Tralhão, Paulo Donato, Alfredo Gil Agostinho, Francisco Castro e Sousa, Filipe Caseiro Alves, Júlio Leite

4. **Resumo submetido**: "Early Functional Response after Portal Vein Embolization – Difference between Future Liver Remnant and Embolized Liver Relative Enhancement as a Marker of Improved Hepatocellular Reserve"- a aguardar publicação na HPB Journal – Revista indexada, de Fator de Impacto 3.29 (2016).

Mariana Duque, Henrique Alexandrino, Henrique Donato, Ricardo Martins, Marco Serôdio, José Guilherme Tralhão, Paulo Donato, Alfredo Gil Agostinho, Francisco Castro e Sousa, Filipe Caseiro Alves, Júlio Leite

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