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Original Article

Measurement of Regional Liver Function with Dynamic Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid-Enhanced Magnetic Resonance Imaging

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Abstract

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Background: Assessing regional liver function is crucial in patients scheduled for liver resection to support risk assessment and anticipate post-hepatectomy liver failure [PHLF].

The aim of the work: This study aimed to determine the utility of gadoxetic acid-enhanced MRI as a non-invasive, imaging-based method for evaluating regional liver function.

Patients and Methods: In this retrospective analysis, 36 patients who underwent serial gadoxetic acid-enhanced MRI scans were included. Imaging was performed prior to and after portal vein embolization [PVE], as well as following extended right hemihepatectomy. Signal intensity [SI] and relative enhancement [RE] during the hepatobiliary phase were measured to determine the most reliable indicator of regional hepatic function.

Results: A notable reduction in relative enhancement of the right liver lobe [RLL] was observed 14 days [RE = 0.49, P < 0.005] and 28 days post-PVE [RE = 0.50, P = 0.005], compared to pre-PVE levels [RE = 0.64]. Conversely, the left liver lobe [LLL] exhibited a significant increase in RE 28 days post-PVE [RE = 0.70] compared to baseline [RE = 0.62, P = 0.040]. Pearson correlation analysis demonstrated a significant positive relationship between LiMAx values and RE in the RLL before PVE [r = 0.452, P < 0.05], as well as in the LLL both pre-PVE [r = 0.399, P < 0.05] and postoperatively [r = 0.488, P < 0.05].

Conclusion: Gadoxetic acid-enhanced MRI offers a reliable, imaging-based approach to assess regional liver function and can effectively estimate the functional reserve of hepatic segments.

Keywords: Dynamic contrast-enhanced MRI; Gadoxetic acid-enhanced MRI; Future liver remnant volume; Liver function tests.

INTRODUCTION

The liver, as a central metabolic organ, performs a wide array of vital functions including glycogen and vitamin storage, synthesis of various proteins and clotting factors, metabolism and detoxification of substances such as bilirubin and drugs, as well as immune regulation [1].

In clinical practice, liver function assessment is crucial for the management of patients with diffuse liver disorders, malignancies, and those undergoing liver-directed therapies. In particular, accurate evaluation of hepatic function is essential in patients scheduled for major liver resections and in the monitoring of liver transplant recipients [1,2].

Liver function tests - such as the 13C-methacetin breath test [LiMAx], indocyanine green [ICG] clearance, and clinical scoring systems like the Child-Pugh classification and MELD score - are designed to evaluate overall hepatic performance. However, they fall short in assessing segmental or regional liver function, which is especially relevant in conditions marked by uneven liver involvement, such as primary sclerosing cholangitis, unilateral cholestasis, or after portal vein embolization [PVE] [3, 4].

In the setting of liver resection, the need for precise regional functional evaluation has grown significantly due to the increasing complexity and extent of surgical interventions. Accurately determining the liver's functional reserve is key for effective risk assessment and in predicting the likelihood of post-hepatectomy liver failure [PHLF] [5-7].

Modern imaging techniques now offer not only volumetric assessment but also functional insights. Imaging-based liver function tests have emerged as a valuable tool, enabling quantification of hepatic function at the segmental or lobar level. These methods utilize intravenously administered agents that are selectively taken up by hepatocytes and subsequently metabolized or excreted into the biliary system. By analyzing the temporal dynamics of these processes, both global and regional liver function can be assessed [1, 8].

PATIENTS AND METHODS

Study design and population:

This retrospective study included 36 consecutive patients who underwent right hemihepatectomy following portal vein embolization [PVE] between March 2014 and September 2015. All patients were evaluated using serial gadoxetic acid-enhanced MRI at four time points: before PVE, 14 days and 28 days post-PVE, and after hepatectomy.

Eligible patients were those who had undergone PVE prior to extended right hepatectomy and had completed gadoxetic acid-enhanced MRI scans at all the predefined time intervals. Additional inclusion criteria required patients to be 18 years of age or older and to have no prior history of systemic chemotherapy, liver surgery, liver transplantation, or any form of locoregional treatment for liver tumors. Only patients who completed the full imaging protocol were considered for analysis.

Patients were excluded if they had a history of systemic chemotherapy, previous liver resection, transplantation, or locoregional liver interventions. Additional exclusion criteria included non-diagnostic image quality due to severe artifacts, contraindications to contrast agent administration [including a known allergy to gadoxetic acid or a glomerular filtration rate below 30 ml/min/1.73 m²], and any absolute contraindications to MRI such as non-compatible implanted devices like pacemakers, defibrillators, or cochlear implants. Relative contraindications, such as the presence of ferromagnetic foreign bodies, unfavorable tattoos or vascular clips, and severe claustrophobia, were also considered. The study protocol received approval from the institutional review board, and the requirement for written informed consent was waived due to the retrospective design.

Portal Vein Embolization and Extended Right Hemi-hepatectomy:

PVE was carried out by percutaneous transhepatic access to the right portal vein under ultrasound guidance. Embolization of the right liver lobe [segments V–VIII] was achieved using a combination of embolic particles and coils. Approximately 30 days after the procedure, patients underwent an extended right hemihepatectomy.

MRI Protocol and Image Analysis:

All patients underwent gadoxetic acid-enhanced MRI scans at four distinct time points: prior to PVE, 14 and 28 days after PVE, and 10 days following the hepatic resection. Imaging was performed using a 1.5-T MRI scanner [Siemens Magnetom Avanto, Siemens Healthcare]. T1-weighted transverse images were acquired using a volume-interpolated breath-hold examination [VIBE] sequence. The imaging parameters included a repetition time [TR] of 4.26 ms, an echo time [TE] of 1.93 ms, a flip angle of 30°, a slice thickness of 3 mm, and a matrix of 256 × 127. The protocol covered the entire liver with 60–80 slices and a field of view adjusted between 255–300 mm and 340–400 mm. Contrast enhancement was achieved through intravenous administration of gadoxetic acid [Primovist, Bayer Pharma] at a dose of 0.1 ml/kg body weight, with imaging repeated 20 minutes post-injection.

Image analysis was performed using Visage 7.1.4 software [Visage Imaging]. Signal intensity [SI] was recorded from three circular regions of interest [ROIs], each approximately 2 cm in diameter, within both the left liver lobe [LLL] and the right liver lobe [RLL]. Measurements were taken before contrast administration [SI_unenhanced] and 20 minutes after [SI_delayedphase]. Care was taken to place ROIs in areas free from major blood vessels, bile ducts, and tumor lesions.

Relative enhancement [RE] was calculated using the following formula: RE = [SI_delayedphase − SI_unenhanced] / SI_unenhanced

LiMAx test - 13C-methacetin breath test [13C-MBT]:

LiMAx test results were collected at three of the four study time points: prior to PVE, 14 days after PVE, and 10 days following extended right hemihepatectomy. The test was conducted within 24 hours of the corresponding MRI scan, adhering to the recommendations outlined by Stockmann et al.[9-10] A LiMAx value exceeding 315 µg/kg/h was interpreted as indicative of preserved hepatic function, whereas values below 140 µg/kg/h were considered to reflect severely impaired liver function, representing a contraindication for surgery.[9-10]

Laboratory Parameters:

Serum levels of total bilirubin [mg/dL] and albumin [g/dL] were retrospectively obtained for each of the four time points, with collection occurring within one month before the corresponding MRI examination.

Statistical Analysis:

Continuous data were expressed as mean ± standard deviation [SD]. Variations in signal intensity [SI], relative enhancement [RE], serum bilirubin, albumin, and LiMAx values across the different time points were assessed using repeated measures ANOVA. For comparisons between specific time points, paired t-tests were employed for data with a normal distribution, while the Wilcoxon signed-rank test was used for non-normally distributed data. Correlation analyses were performed using Pearson's correlation coefficient. All statistical computations were executed using SPSS Statistics version 25 [IBM] and R version 3.5.1 [R Foundation for Statistical Computing]. A two-tailed P-value < 0.05 was considered to indicate statistical significance.

RESULTS

Patient Characteristics:

The study cohort consisted of 36 patients with a mean age of 62 ± 10.8 years [range: 41–82 years], including 21 males [mean age: 65 ± 10.4 years; range: 49–82 years] and 15 females [mean age: 61.4 ± 9.9 years; range: 41–77 years]. The most frequent indication for extended right hemihepatectomy was cholangio-carcinoma, observed in 19 patients -13 with hilar cholangiocarcinoma and 6 with intrahepatic cholangiocarcinoma - followed by colorectal liver metastases, found in 11 patients. All diagnoses were confirmed through histopathological examination. A summary of patient characteristics is provided in **Table [1]**.

Unenhanced Signal Intensity [SI]:

Prior to contrast administration, Signal intensity in the right liver lobe [RLL] was significantly higher than in the left liver lobe [LLL] at all measured time points: before PVE [236.21 vs. 202.03, P = 0.040], 14 days post-PVE [244.03 vs. 206.14, P < 0.005], and 28 days post-PVE [250.31 vs. 211.90, P < 0.005]. However, no significant changes in unenhanced SI were detected within each lobe across the different time points [**Tables 2 and 3**].

Signal Intensity in the Hepatobiliary Phase [HBP]:

In the hepatobiliary phase, the RLL consistently showed higher SI than the LLL both before PVE [398.46 vs. 331.60, P = 0.005] and at 14 days post-PVE [375.61 vs. 344.93, P = 0.004]. Additionally, a significant decline in RLL SI was observed 14 days after PVE when compared to baseline [P = 0.016]. For the LLL, a notable reduction in HBP SI was seen 10 days after hepatectomy when compared to all earlier time points: before PVE [P = 0.005], 14 days post-PVE [P < 0.005], and 28 days post-PVE [P < 0.005] [**Tables 2 and 3**].

Relative Enhancement [RE]:

At baseline, RE in the RLL was slightly higher than in the LLL, though this difference was not statistically significant [0.64 vs. 0.62, P = 0.237]. However, after PVE, RE in the RLL was significantly lower than in the LLL at both 14 days [0.49 vs. 0.67, P < 0.005] and 28 days [0.50 vs. 0.70, P < 0.005] [Tables 2 and 3, Figure 1]. Within the RLL, RE significantly decreased at 14 days [0.49, P < 0.005] and 28 days post-PVE [0.50, P= 0.005] compared to pre-PVE levels [0.64]. No significant change was observed between the 14- and 28-day post-PVE RE values [P = 0.176]. In the LLL, RE significantly increased at 28 days post-PVE compared to pre-PVE [0.70 vs. 0.62, P = 0.040]. However, after hepatectomy, RE of the LLL significantly declined in comparison to all previous time points: pre-PVE [P = 0.007], 14 days post-PVE [P < 0.005], and 28 days post-PVE [P < 0.005] **[Tables 2 and 3, Figure 1].**

Correlation between RE and Patient Age:

There was a significant negative correlation between patient age and RE in the RLL prior to PVE [r = -0.355, P = 0.037]. Following surgery, a similar inverse relationship was found between age and SI in both the unenhanced and hepatobiliary phases, as well as with RE in the LLL [r = -0.436, -0.607, -0.573; P = 0.026, 0.001, 0.002, respectively].

LiMAx-Test Results:

LiMAx test values significantly decreased following hepatectomy when compared to values measured before PVE, and at both 14 and 28 days post-PVE [P < 0.005]. No other significant differences were observed between the remaining time points [Tables 4 and 5]. Pearson correlation analysis revealed a positive correlation between the LiMAx test and RE of the RLL before PVE [r = 0.452, P < 0.05], as well as with the LLL RE both pre-PVE [r = 0.399, P < 0.05] and postoperatively [r = 0.488, P < 0.05].

Table [1]: Baseline patient demographics

Variable	Mean ± SD [min – max]
Gender [Male/female]	21/15
Age [years]	62±10.8 [41-82]
Indications of PVE and extended right hemihepatectomy:	
• **Colorectal liver metastasis**	11 [30.6%]
• **Hilar cholangiocarcinoma [Klatskin tumour]**	13 [36.1%]
• **Intrahepatic cholangiocellular carcinoma [CCC]**	6 [16.7%]
• **Gallbladder carcinoma**	4 [11.1 %]
• **Hepatocellular carcinoma [HCC]**	1 [2.8%]
• **Focal nodular hyperplasia [FNH]**	1 [2.8%]

Table [2]: Descriptive analysis of signal intensity and relative enhancement of the liver in all 4 time points of the study.

			Mean	Std. Deviation	Minimum	Maximum
RLL	**SI unenhanced**	**Pre-PVE**	236.21	38.52	170.60	376.80
		14d-post PVE	244.03	40.93	146.10	347.67
		28d-post PVE	250.31	36.96	194.93	331.07
	SI HBP	**Pre-PVE**	398.46	81.79	239.83	601.30
		14d-post PVE	375.61	57.99	256.87	465.23
		28d-post PVE	360.59	70.52	269.60	596.00
	RLL RE	**Pre-PVE**	0.64	0.19	0.26	1.06
		14d-post PVE	0.49	0.16	0.14	0.86
		28d-post PVE	0.50	0.14	0.28	0.82
LLL	**SI unenhanced**	**Pre-PVE**	202.03	32.04	141.70	291.73
		14d-post PVE	206.14	32.99	148.13	286.53
		28d-post PVE	211.90	34.66	168.50	310.77
		10d-post OP	195.76	39.57	143.23	299.50
	SI HBP	**Pre-PVE**	331.60	64.84	213.97	507.83
		14d-post PVE	344.93	66.46	227.53	488.23
		28d-post PVE	359.84	73.35	260.20	601.03
		10d-post OP	295.55	79.58	180.50	475.53
	LLL RE	**Pre-PVE**	0.62	0.14	0.23	0.92
		14d-post PVE	0.67	0.16	0.20	0.97
		28d-post PVE	0.70	0.18	0.41	1.14
		10d-post OP	0.48	0.21	0.13	0.95
Whole liver	**SI unenhanced**	**Pre-PVE**	218.34	34.28	157.88	331.55
		14d-post PVE	224.08	35.63	154.32	315.62
		28d-post PVE	230.11	34.45	183.99	320.76
	SI HBP	**Pre-PVE**	363.41	72.44	226.53	552.59
		14d-post PVE	352.45	61.28	241.76	471.01
		28d-post PVE	367.30	70.29	270.93	598.51
	RE	**Pre-PVE**	0.65	0.20	0.24	0.94
		14d-post PVE	0.57	0.14	0.16	0.90
		28d-post PVE	0.59	0.15	0.34	0.97

Table [3]: Pairwise comparison of signal intensity and relative enhancement measurements between different time points of the study.

		P value		
		SI unenhanced	**SI HBP**	**RE**
RLL	**Pre- vs. 14d-post PVE**	0.230	**0.016**	**< 0.005**
	Pre- vs. 28d-post PVE	0.235	0.141	**0.005**
	14d- vs. 28d-post PVE	0.911	0.443	0.176
LLL	**Pre- vs. 14d-post PVE**	0.880	0.366	0.087
	Pre- vs. 28d-post PVE	0.809	0.418	**0.040**
	Pre- vs. 10d-post OP	0.173	**0.005**	**0.007**
	14d- vs. 28d-post PVE	0.653	0.862	0.199
	14d- vs. 10d-post OP	0.057	**< 0.005**	**< 0.005**
	28d- vs. 10d-post OP	0.167	**< 0.005**	**< 0.005**
RLL vs. LLL	**Pre-PVE**	**0.040**	**0.005**	0.237
	14d-post PVE	**< 0.005**	**0.004**	**< 0.005**
	28d-post PVE	**< 0.005**	0.152	**< 0.005**

Table [4]: LiMAx test values collected at the four measuring points.

	pre-PVE	14d-post-PVE	28d-post-PVE	10d-post-op
LiMAx value [Mean±SD] [μg/h/kg]	425 ± 113.6	461 ± 158.9	437 ± 119.7	148 ± 44.3

Table [5]: Pairwise comparison of LiMAx test between different measuring time points.

		P value
LiMAx	Pre- vs. 14d-post PVE	0.141
	Pre- vs. 28d-post PVE	0.152
	Pre- vs. 10d-post OP	**< 0.005**
	14d- vs. 28d-post PVE	0.114
	14d- vs. 10d-post OP	**< 0.005**
	28d- vs. 10d-post OP	**< 0.005**

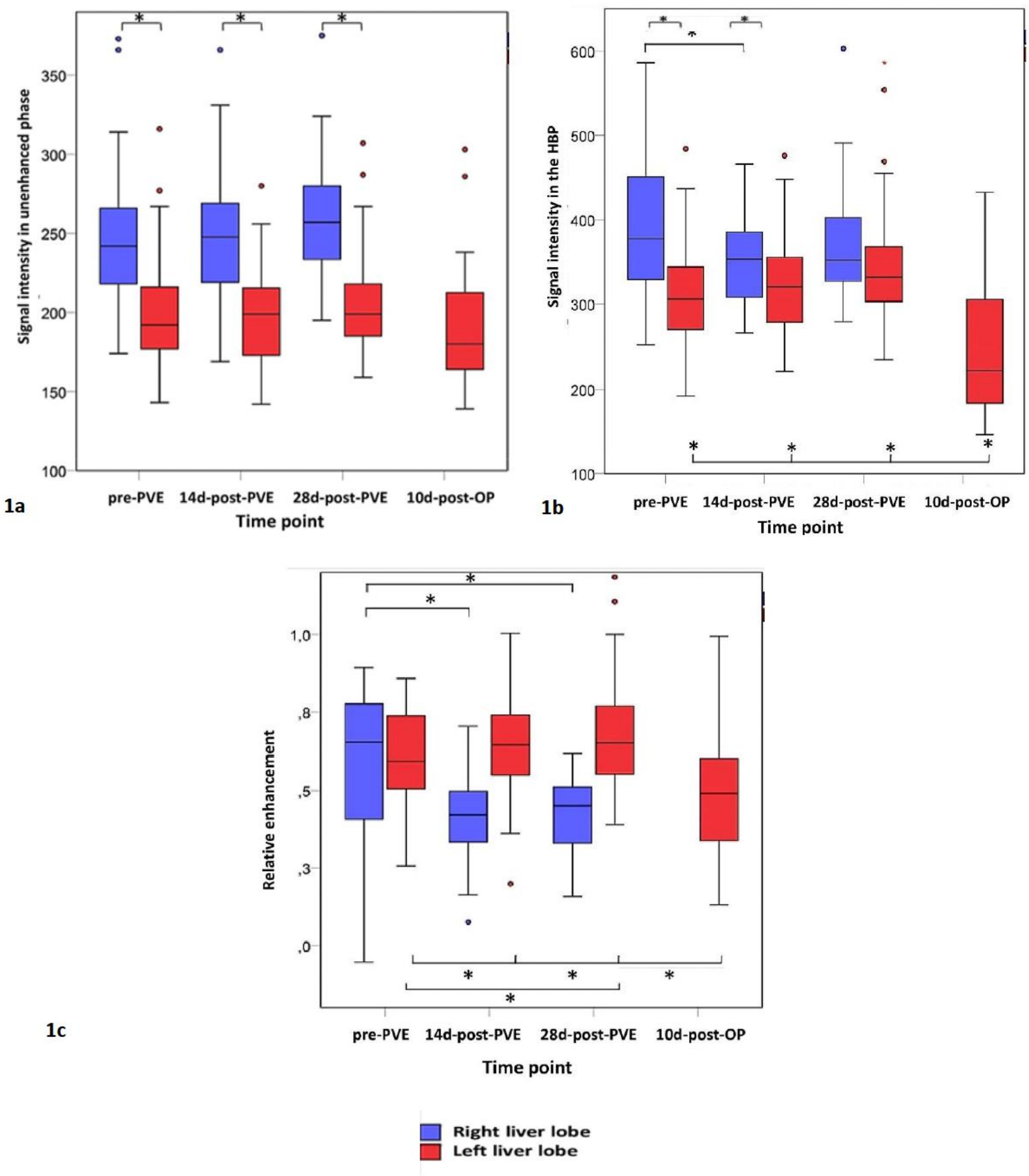

Figure [1]: Signal intensity in the unenhanced phase [**1a**] and hepatobiliary phase [**1b**] as well as relative enhancement [**1c**] of the RLL and LLL before PVE, 14 days after PVE, 28 days after PVE and 10 days after hepatectomy [* = P < 0.05]

DISCUSSION

Assessing liver function is crucial in managing patients with chronic liver disease, liver tumors, or those being considered for a liver transplant. It is especially important before liver surgery, which has become more advanced and extensive due to ongoing advancements in surgical, radiologic, and oncologic techniques. However, more radical liver resections also increase the risk of post-hepatectomy liver failure [PHLF] [1, 11].

In contrast to traditional laboratory tests and clinical scoring systems, imaging-based methods enable the evaluation of regional liver function. Unlike nuclear medicine techniques such as scintigraphy, gadoxetic acid-enhanced MRI offers superior spatial and temporal resolution, and does so without the use of ionizing radiation. Furthermore, it integrates more seamlessly into routine preoperative imaging protocols [1, 12].

This study shows that gadoxetic acid-enhanced MRI is useful for assessing liver function on a segmental level. Notably, even without complex post-processing or advanced functional mapping, simple signal intensity [SI] measurements provided meaningful insights into regional hepatic function. The study demonstrated that while SI in the pre-contrast [unenhanced] phase remained relatively stable across the four evaluated time points, there was a progressive decline in hepatobiliary phase [HBP] SI in the right liver lobe [RLL] following PVE. This pattern may reflect a gradual decline in functional capacity of the embolized lobe.

These observations are in line with prior research by Akiba et al. [13], who retrospectively analyzed changes in SI and liver volume before and after PVE using gadoxetic acid-enhanced MRI. Their study revealed a significant post-PVE decrease in SI contrast between the left liver lobe [LLL] and RLL [$P < 0.01$], alongside a negative correlation between the percentage of future liver remnant [%FLR] and both the SI contrast and the SI ratio [defined as the change in SI contrast from pre- to post-PVE]. These findings further reinforce the utility of direct SI measurements in predicting regional hepatic function, particularly in the future liver remnant.

The ability of gadoxetic acid-enhanced MRI to reflect segmental functional changes in response to interventions like PVE underlines its potential as a reliable, non-invasive imaging-based liver function test. This capability is particularly valuable in preoperative planning for major liver resections, where regional disparities in function can have a critical impact on patient outcomes.

Analysis of RE during the hepatobiliary phase revealed a consistent increase in RE within the LLL, representing the FLR, following PVE. The most notable rise was observed at the 14-day mark post-PVE. Interestingly, the absence of significant RE changes between 14 and 28 days suggests that the most substantial functional enhancement of the FLR occurs within the first two weeks after embolization. This finding supports the potential benefit of scheduling surgery earlier after PVE, which may offer clinical advantages. Early resection could help mitigate the risk of tumor progression—an important consideration given that PVE-induced liver regeneration has also been associated with accelerated tumor growth. Several studies have reported that the regenerative stimuli initiated by PVE can inadvertently promote tumor advancement, potentially compromising resectability and leading to missed surgical opportunities [14-16].

Our results were in agreement with the study by **Geisel *et al.*** [17]. In this prospective study, they investigated the changes in regional liver function between the RLL and LLL following PVE, using gadoxetic acid-enhanced MRI in 10 patients who were scheduled for extended right hemihepatectomy. The hepatic uptake index [HUI] and RE were calculated for both the embolized RLL and the LLL before and 14 days after PVE. The results showed a significant increase in HUI and RE in the LLL, while the RLL exhibited a decrease in both parameters 14 days post-PVE. Their findings indicated a marked shift in gadoxetic acid uptake, which could reflect the redirected portal venous blood flow and a corresponding shift in functional capacity from the RLL to the LLL, observable as early as 14 days after PVE.

In a similar study by **Geisel *et al.***, gadoxetic acid-enhanced MRI measurements of RE and HUI in the RLL and LLL after PVE were compared with ^{99m}Tc-mebrofenin hepatobiliary scintigraphy [HBS] in 14 patients [2]. Their study found a significant correlation between mebrofenin uptake and both RE and HUI values for the LLL and RLL, which supports the current study's findings that gadoxetic acid-enhanced MRI can effectively assess regional liver function. Moreover, the significant correlation between gadoxetic acid-based measures and mebrofenin uptake in HBS further suggests that gadoxetic acid-enhanced MRI might offer advantages over traditional HBS, particularly given its lack of ionizing radiation.

An additional finding in our study was the negative correlation between patient age and relative enhancement [RE], which aligns with previous research by **Theilig *et al.*** [18], who observed a similar trend in a larger cohort [$n = 554$]. This association may be explained by age-related changes in hepatic drug metabolism, resulting in reduced uptake of gadoxetic acid and, consequently, lower RE in older individuals. Another potential explanation could be the natural decline in liver function with advancing age, a phenomenon that can occur even in patients without pre-existing liver disease [19].

Further studies are needed to determine whether this age-related effect is primarily due to a decline in hepatic functional reserve in the elderly.

Regarding the laboratory parameters investigated, significant changes were only observed when comparing postoperative values with preoperative ones. However, the ability to assess functional changes in the LLL and RLL during the course of treatment, particularly after PVE, was limited. This highlights a key limitation of laboratory parameters, as they provide only a global estimate of liver function. In our study, RE of the LLL after hepatectomy, representing the liver remnant, showed a negative correlation with total bilirubin, while albumin demonstrated a positive correlation with RE of the LLL 14 days following PVE. These findings align with results from studies by **Cho et al.** [20] and **Talakic et al.** [21], further supporting the notion that RE can serve as a useful indicator for assessing liver function.

In terms of dynamic LFTs, we selected the LiMAx test, which is currently regarded as the gold standard among dynamic LFTs [9-10].

Like biochemical parameters, the LiMAx test is a global liver function test, capable of detecting overall functional deterioration after liver resection. However, it cannot capture the temporal changes in function of the LLL and RLL following PVE. Notably, RE of the LLL showed a significant correlation with LiMAx values both before PVE and after surgery. This finding further validates the use of RE in gadoxetic acid-enhanced MRI as a reliable marker for assessing liver function.

Limitations: Our study has some limitations. The retrospective nature of the design and the relatively small sample size [n = 36] may reduce the strength and generalizability of our findings. We also did not evaluate the influence of kidney function on the uptake and excretion of gadoxetic acid, which is eliminated equally by the kidneys [50%] and liver [50%]. Consequently, any existing renal impairment could lead to a slight increase in hepatic parenchymal enhancement. However, to minimize this effect, our study intentionally excluded patients with renal dysfunction.

In conclusion, gadoxetic acid-enhanced MRI offers a promising method for evaluating liver function, specifically in terms of estimating the regional functional capacity of the liver.

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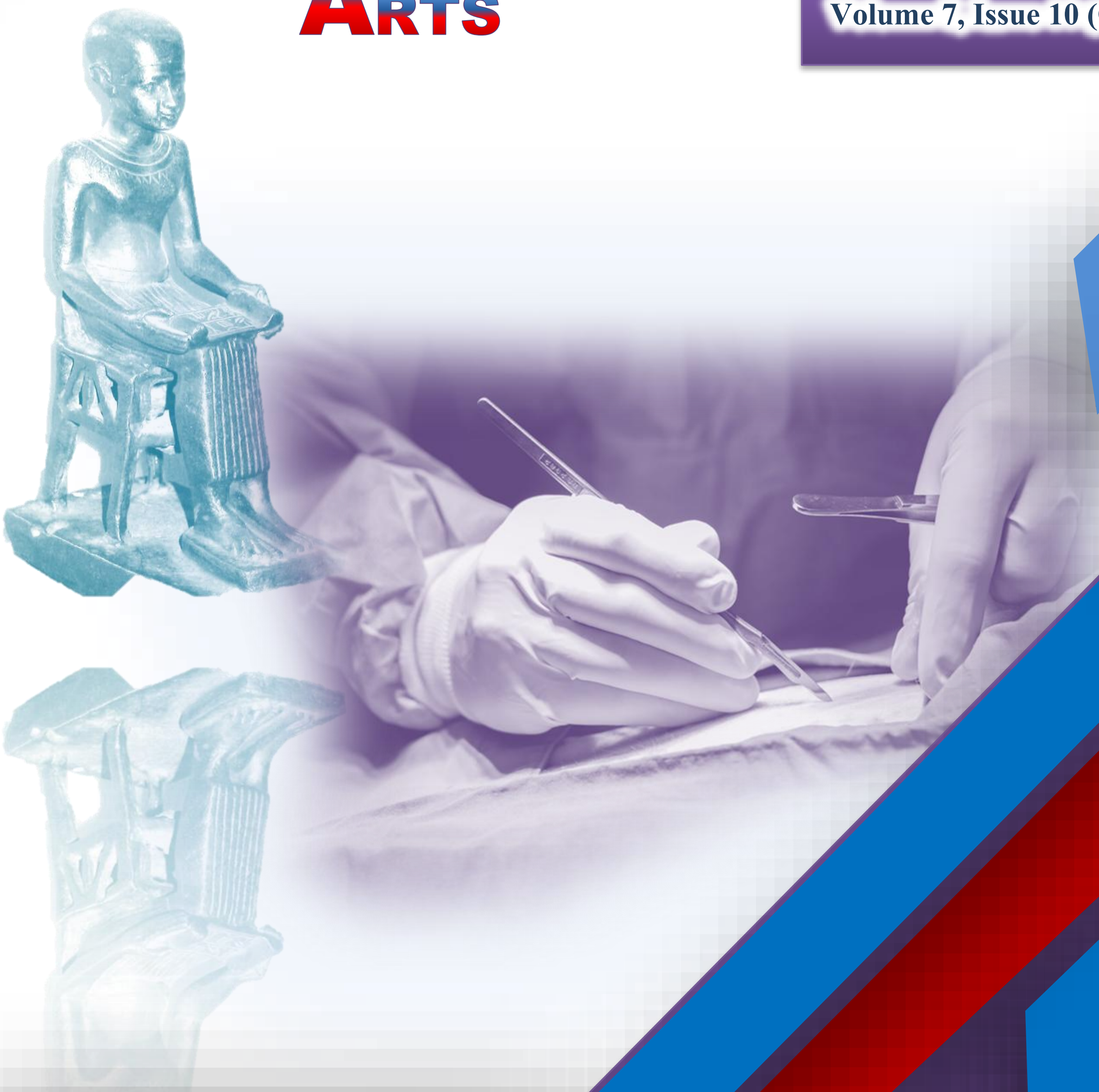

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