Multivariable Analysis of Clinical Influence Factors on Liver Enhancement of Gd-EOB-DTPA-Enhanced 3T MRI

Multivariable Analyse klinischer Einflussfaktoren auf die Signalintensität bei Gd-EOB-DTPA 3T-MRT der Leber

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Key words

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Bibliography

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Abstract

Purpose: The purpose of this study was to identify clinical factors influencing Gd-EOB-DTPA liver uptake in patients with healthy liver parenchyma.

Materials and Methods: A total of 124 patients underwent contrast-enhanced MRI with a hepatocyte-specific contrast agent at 3 T. T1-weighted volume interpolated breath-hold examination (VIBE) sequences with fat suppression were acquired before and 20 minutes after contrast injection. The relative enhancement (RE) between plain and contrast-enhanced signal intensity was calculated. Simple and multiple linear regression analyses were performed to evaluate clinical factors influencing the relative enhancement. Patients were subdivided into three groups according to their relative liver enhancement (HRE, RE ≥ 100 %; MRE, 100 % > RE > 50 %; NRE, RE ≤ 50 %) and were analyzed according to the relevant risk factors.

Results: Simple regression analyses revealed patient age, transaminases (AST, ALT, GGT), liver, spleen and delta-liver volume (the difference between the volumetrically measured liver volume and the estimated liver volume based on body weight) as significant factors influencing relative enhancement. In the multiple analysis the transaminase AST, spleen and delta liver volume remained significant factors influencing relative enhancement. Delta liver volume showed a significant difference between all analyzed groups.

Conclusion: Liver enhancement in the hepatobiliary phase depends on a variety of factors. Body weight-adapted administration of Gd-EOB-DTPA may lead to inadequate liver enhancement after 20 minutes especially when the actual liver volume differs from the expected volume.

Key Points:

- Differences between actual and expected liver volume can cause inadequate liver enhancement after 20 min.
- A liver volume-adapted dose of Gd-EOB-DTPA may help to improve liver enhancement.

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Zusammenfassung

Ziel: Analyse klinischer Faktoren, welche die Aufnahme von Gd-EOB-DTPA in einem Patientenkollektiv ohne Leberparenchymschädigungen beeinflussen.

Material und Methoden: 124 Patienten erhielten eine 3T-MRT-Untersuchung mit leberspezifischem Kontrastmittel zur sekundären Leberläsionsabklärung. Anhand T1-gewichteter VIBE-Sequenzen der Leber mit Fettunterdrückung wurde die relative Signaländerung (RE) zwischen nativer und hepatobiliärer Phase (20 min) evaluiert. Einfache und multiple lineare Regressionsanalysen wurden durchgeführt, um klinische Einflussfaktoren auf die Signaländerung zu bestimmen. Im Anschluss wurden die Patienten anhand der berechneten relativen Signalveränderung in drei Gruppen aufgeteilt (HRE, RE ≥ 100 %; MRE, 100 % > RE > 50 %; LRE, RE ≤ 50 %) und bezüglich der relevanten Risikofaktoren untersucht.

Ergebnisse: Die einfache Regressionsanalyse zeigte eine Korrelation zwischen relativer Signalverstärkung und dem Patientenalter, dem Leber- und dem Milzvolumen, dem sog. Deltalebervolumen

(errechnete Abweichung zwischen dem gemessenen und dem gewichtsbasiert geschätzten Lebervolumen), sowie den Transaminasen AST, ALT, GGT. In der multiplen Analyse verblieben das Milz- und das Deltalebervolumen, sowie die Transaminase AST als signifikante Einflussfaktoren auf die Signalveränderung. Das Deltalebervolumen zeigte als einziger Parameter einen signifikanten Unterschied zwischen allen gebildeten Subgruppen.

Schlussfolgerungen: Die Kontrastierung der Leber in der hepatobiliären Phase ist von verschiedenen Faktoren abhängig. Wird Gd-EOB-DTPA alleine über das Patientengewicht dosiert, so kann dies zu einer inadäquaten Kontrastierung führen, besonders wenn das Lebervolumen nicht in Korrelation zu dem Körpergewicht steht.

Introduction

MRI imaging of the liver plays a decisive role in the clinical routine. It has become established in recent years as a good, noninvasive method for the detection and characterization of focal and diffuse liver lesions. The use of liver-specific contrast agents allows general tissue perfusion evaluation in the vascular phases and provides specific information about hepatocytes.

Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a widely used contrast agent with selective liver-specific uptake [1, 2]. After the vascular phases, there is liver-specific accumulation with an increase in signal intensity in T1-weighted sequences. The specific accumulation within the liver can be observed after 10 minutes up to at least 2 hours with a wash-in period of 20 minutes being used in the clinical routine [3, 4]. As a result of this additional hepatobiliary phase (HBP), liver-specific contrast agents are particularly helpful in the detection and characterization of liver lesions [5 – 7].

From the clinical routine it is generally known that there are cases in which there is only minimal contrast enhancement in the HBP after 20 minutes. Studies have shown that the accumulation of Gd-EOB-DTPA in the liver parenchyma in the case of liver fibrosis and cirrhosis is slowed or reduced [8 – 13] and consequently adequate diagnosis of liver lesions could be limited.

To our knowledge, there are no studies regarding the inadequate uptake of Gd-EOB-DTPA in a patient collective without liver parenchyma damage. The goal of this study was to analyze clinical factors that could influence the uptake of Gd-EOB-DTPA.

Materials and Methods

Patient collective

In the period from May 2012 to February 2014, 553 weight-adapted Gd-EOB-DTPA-enhanced MRI examinations were performed. 286 patients were excluded from this study due to diffuse liver parenchyma damage or primary liver lesions. In addition, patients with treatment damaging the liver parenchyma (n = 115), motion artifacts, or incomplete examination (n = 28) were excluded from this study. In total, 124 patients were included in this retrospective study. These patients underwent Gd-EOB-DTPA-enhanced MRI examination for secondary liver lesion clarification. The study was approved by the local ethics committee of the medical faculty of the university. **Table 1** shows the patient characteristics for this study.

MRI

All examinations were performed on a clinical 3 T system (Magnetom Skyra, Siemens Healthcare). A combination of body and spine coil elements (18-channel body matrix coil, 24-channel spine matrix coil) was used for signal detection. A T1-weighted VIBE (volume interpolated breath hold examination) sequence with fat suppression was performed during a breath-hold:

	all patients (n = 124)	HRE (n = 52)	MRE (n = 63)	LRE (n = 9)
age (years)	59.9 ± 14.6	57.3 ± 14.7	61.2 ± 15.1	66.4 ± 7.8
gender, n (%)				
– male	67 (54)	27 (52)	34 (54)	6 (67)
– female	57 (46)	25 (48)	29 (46)	3 (33)
weight (kg)	74.7 ± 14.2	77.1 ± 15.2	72.4 ± 13.1	77.0 ± 14.7
height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
liver volume (ml)	1890.9 ± 475.4	1789.3 ± 358.6	1861.4 ± 363.6	2683.9 ± 921.8
spleen volume (ml)	386.1 ± 222.8	321.5 ± 137.0	410.9 ± 248.3	585.2 ± 299.1
Δ liver volume (ml)	316.1 ± 441.9	170.49 ± 324.01	329.0 ± 328.7	1066.8 ± 849.7
aspartate aminotransferase (AST) (U/l)	22.5 ± 8.6	21.2 ± 7.9	22.5 ± 8.6	28.9 ± 10.4
alanine aminotransferase (ALT) (U/l)	27.2 ± 9.9	29.4 ± 10.0	25.9 ± 9.7	23.0 ± 8.6
gamma glutamyl transferase (GGT) (U/l)	101.9 ± 111.5	79.4 ± 59.5	91.8 ± 70.8	322.9 ± 292.5
bilirubin (total) (mg/dl)	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.3	0.9 ± 0.3
thrombocytes (/nl)	221.8 ± 115.0	229.0 ± 78.5	208.6 ± 92.7	271.6 ± 304.7
estimated glomerular filtration rate (eGFR) (ml/min/1.73m2)	98.0 ± 24.1	96.0 ± 23.2	99.1 ± 25.5	101.2 ± 20.4

HRE: high relative enhancement; MRE: medium relative enhancement; LRE: low relative enhancement

Table 1 Patient characteristics in the individual subgroups. Data are shown as average ± standard deviation.

Repetition time (TR): 3.09 ms; echo time (TE): 1.16 ms; flip angle: 9°; parallel imaging factor: 2; slices: 64; reconstructed voxel size: 1.3 mm × 1.3 mm × 3.0 mm; measured voxel size: 1.7 mm × 1.3 mm × 4.5 mm; acquisition time: 14 sec.
The entire liver was visualized with this sequence before (unenhanced) and in the hepatobiliary phase (HBP) (20 min.).
Gd-EOB-DTPA (Primovist; Bayer Schering Pharma AG, Berlin, Germany) was used as the liver-specific contrast agent. All patients received a body weight-adapted dose (0.1 ml/kg body weight) that was administered as a bolus with a flow rate of 1 mL/s with subsequent flushing with 20 ml of NaCL.

Sequence analysis

To calculate the average signal intensity (SI), three circular regions of interest (ROIs) were manually positioned by an examiner in each liver lobe at the same position in the different sequences and were corrected depending on respiratory movement. Special attention was paid to omit visible vessels, liver lesions, or regions with artifacts. The size of the ROIs ranged from 1.0 cm² to 3.5 cm². The thus measured average signal intensity was viewed as representative for the entire liver. The relative signal change (relative enhancement, RE) between the unenhanced phase and the hepatobiliary phase was calculated from this as follows:

$$RE = \frac{SI_{HBP} - SI_{native}}{SI_{native}} \times 100\,(\%)$$

The liver volume and spleen volume were determined in all patients from the MRI dataset with the help of iNtuition-Viewer software (TeraRecon Inc, San Mateo, Calif). Both the spleen volume and liver volume were determined on the basis of the semiautomatic region-growing algorithm and subsequent manual edge correction by an evaluator with hepatobiliary radiology experience. A marker was placed in the target organ in the image datasets of the hepatobiliary phase and this marker was used by the semiautomatic region-growing algorithm for initial segmenting of the organ. In a second work step, this segmenting was manually checked and corrected if necessary.

Statistical analysis

Statistical analysis was performed via IBM SPSS Statistics (Version 21.0.0.1, Chicago, IL). All data are specified as average ± standard deviation if not otherwise specified.
A simple linear regression analysis of clinical factors was used to determine its influence on the relative signal change. In addition to patient characteristics (age, gender, weight, height), the signal intensity baseline ($SI_{(native)}$), the estimated glomerular filtration rate (eGFR) [14], laboratory liver values (GGT, AST, ALT, total bilirubin, number of thrombocytes), as well as the spleen volume and liver volume were examined. The total liver volume (TLV) expected on the basis of the body weight was estimated using the formula described by Vauthey et al. [15]. *TLV = 191.80 + 18.51 × weight [kg]*. The delta liver volume (Δ liver volume) was then calculated as the difference with respect to the actual liver volume: Δ liver volume = *liver volume – TLV*
A multiple linear regression of all significant measured values (inclusion criterion: $p \leq 0.05$) and a pairwise comparison were then performed. For the pairwise comparison, the patients were divided into three groups on the basis of the relative signal change (RE). An RE > 100 % corresponded to a high signal change (high relative enhancement (HRE); n = 52), an RE between 100 % and 50 % corresponded to a medium signal change (medium relative enhancement (MRE); n = 63) and an RE < 50 % corresponded to a low signal change (low relative enhancement (LRE); n = 9). The non-parametric Mann-Whitney test was used to compare the groups to one another. All statistical analyses were two-sided and $p < 0.05$ indicated a significant result.

Results

The simple linear regression analysis (**Table 2**) shows a significant ($p \leq 0.05$) influence on the relative signal change due to the age of the patient, the liver volume, the spleen volume, and the Δ liver volume as well as the following transaminases: Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT).
The result of the multiple linear regression is shown in **Table 3**. In this analysis the spleen volume and Δ liver volume as well as the transferase AST are significant predictors of the relative signal change.
The pairwise comparison (**Fig. 1**) of the significant measured values of the simple linear regression analysis yielded significant differences in the AST and the GGT for the transaminases. The comparison of the HRE and the LRE showed a

Table 2 Resuslts of the simple linear regression analyses with the relative signal change as a dependent variable.

independent variables	B (95 % CI)	r^2	p-value
age (years)	–0.37 (–0.68; –0.06)	0.043	**0.021**
gender	2.35 (–7.01; 11.71)	0.002	0.620
height (m)	–21.32 (–74.99; 32.35)	0.005	0.433
weight (kg)	0.23 (–0.10; 0.55)	0.015	0.173
liver volume (ml)	–0.02 (–0.03; –0.01)	0.102	**≤ 0.001**
spleen volume (ml)	–0.03 (–0.05; –0.01)	0.08	**0.001**
Δ liver volume (ml)	–0.03 (–0.03; –0.02)	0.174	**≤ 0.001**
baseline ($SI_{(native)}$)	0.08 (–0.06; 0.21)	0.01	0.260
aspartate aminotransferase (U/l)	–0.73 (–1.29; –0.17)	0.057	**0.011**
alanine aminotransferase (U/l)	0.48 (0.02; 0.95)	0.033	**0.043**
gamma glutamyl transferase (U/l)	–0.08 (–0.12; –0.04)	0.118	**≤ 0.001**
bilirubin (total) (mg/dl)	–13.93 (–30.62; 2.76)	0.022	0.101
thrombocytes (/nl)	–0.00 (–0.04; 0.04)	0	0.908
estimated glomerular filtration rate (ml/min/1.73 m²)	–0.13 (–0.32; 0.07)	0.014	0.190

B: Regression coefficient, CI: Confidence interval, R^2: Coefficient of determination, p: Level of significance.

Table 3 results of the multiple linear regression analysis with the relative signal change as a dependent variable. The model showed a coefficient of determination (R^2) of 0.352.

independent variables	B (95 % CI)	p-value
age (years)	−0.149 (−0.462; 0.164)	0.347
liver volume (ml)	0.004 (−0.015; 0.023)	0.694
spleen volume (ml)	−0.031 (−0.052; −0.01)	**0.004**
Δ liver volume (ml)	−0.024 (−0.043; −0.004)	**0.017**
aspartate aminotransferase (U/l)	−0.676 (−1.289; −0.062)	**0.031**
alanine aminotransferase (U/l)	0.399 (−0.113; 0.91)	0.125
gamma glutamyl transferase (U/l)	−0.036 (−0.082; 0.011)	0.131

B: Regression coefficient, CI: Confidence interval, p: Level of significance.

significantly increased value in the LRE group for AST (p = 0.038) and GGT (p = 0.021). A significant difference (p = 0.032) between the LRE and MRE group was seen in the case of GGT. No significant difference between the HRE and MRE group could be found.

Further significances resulted for the liver volume and spleen volume in the comparison of the LRE and MRE and in the comparison of the LRE and HRE. Patients in the LRE group had a significantly greater liver volume (2683.9 ± 921.8 ml) and spleen volume (585.2 ± 299.1 ml) compared to the MRE group and the HRE group (**Table 1**, **Fig. 1**).

In the pairwise comparison only the Δ liver volume showed a significant difference between all subgroups (**Fig. 1**). With 1066.8 ± 849.7 ml, patients in the LRE group had the greatest deviation from the calculated liver volume with the patients in the HRE group having the lowest deviation (321.5 ± 137.0 ml). **Fig. 2** shows the effect of the Δ liver volume on the signal intensity in the HBP.

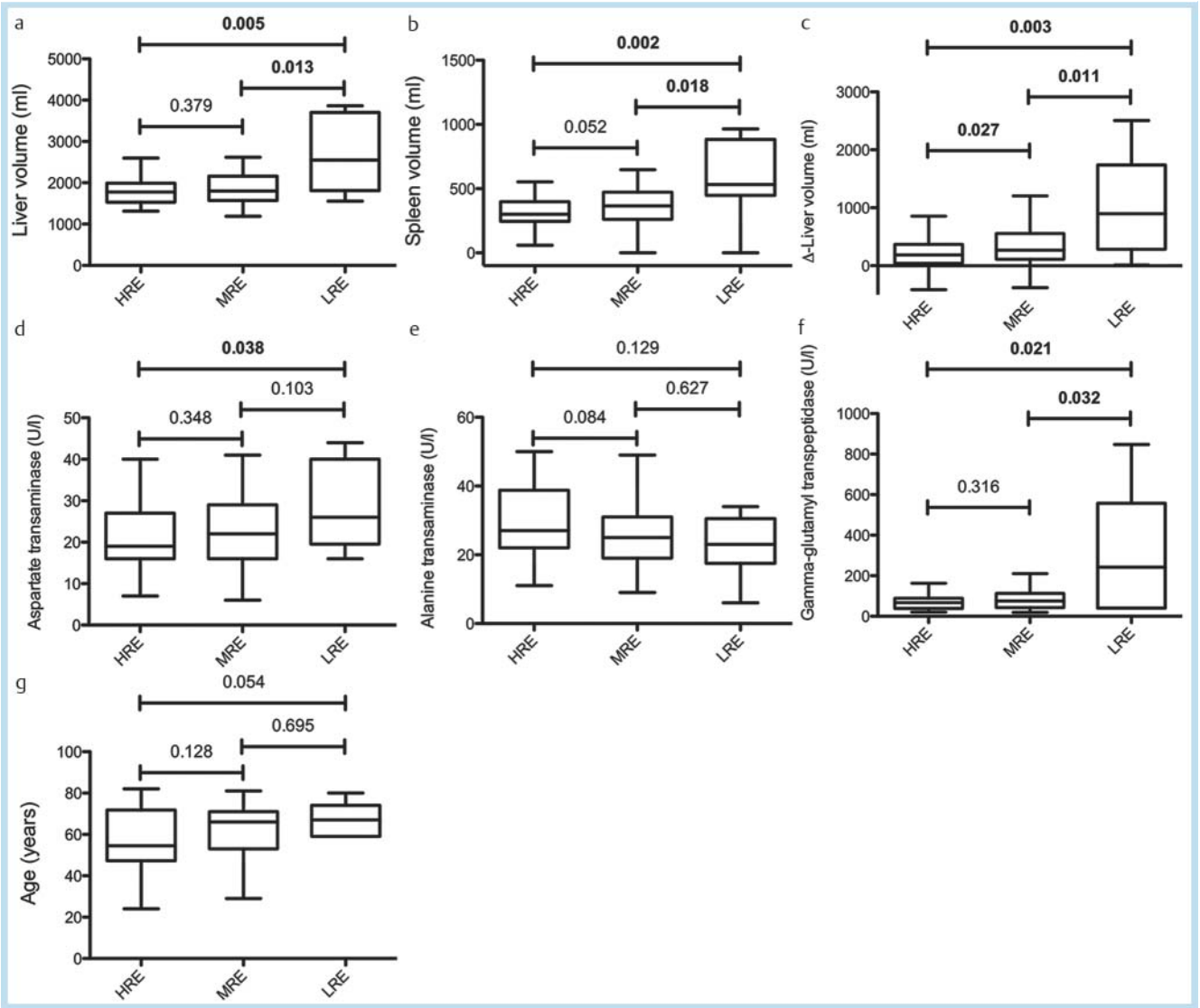

Fig. 1 shows the pairwise comparison of clinical factors between the individual subgroups with the corresponding p-values. The data are shown as box plots with the Tukey algorithm being used in the box and whisker plot. HRE: high relative enhancement, MRE: medium relative enhancement, LRE: low relative enhancement.

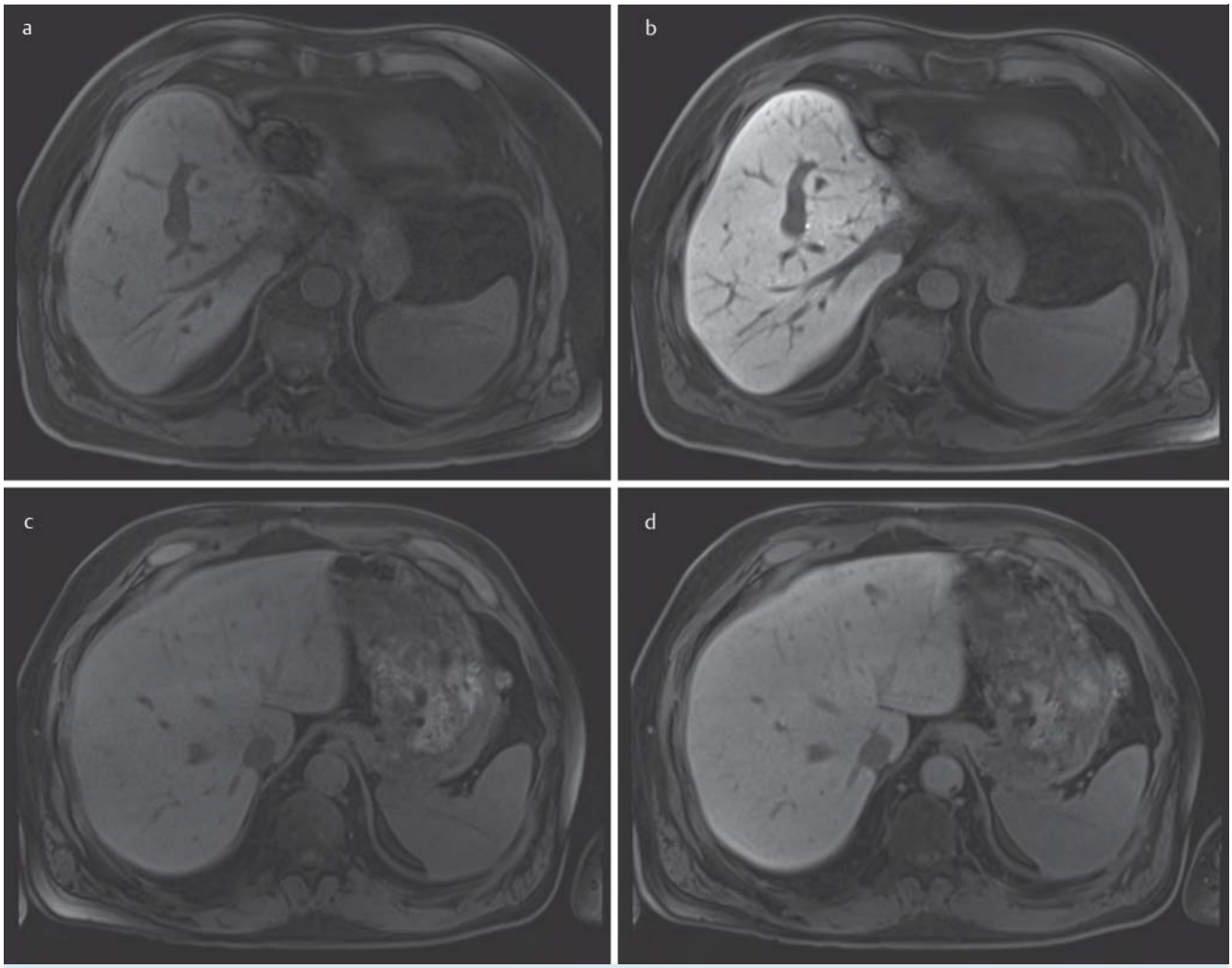

Fig. 2 T1-weighted VIBE sequence with fat suppression of the unenhanced phase **a, c** and the hepatobiliary phase **b, d** after 20 minutes. **a, b** show sequences of a male patient with a weight of 104 kg and a height of 1.89 m. The calculated liver volume was 2117 ml, with the actual liver volume being only 1625 ml. This yielded a Δ liver volume of –492 ml. **c, d** show sequences of a male patient with a weight of 90 kg and a height of 1.72 m. The calculated liver volume was 1858 ml, with the actual liver volume being only 3755 ml. The Δ liver volume was 1897 ml. The average signal intensity was as follows: 213.8 **a**; 492.4 **b**; 199.5 **c**; 297.0 **d**. The relative signal change was 130 % between **a–b** and 49 % between **c–d**.

Discussion

Different imaging methods are available for the daily clinical challenge of detecting and differentiating liver lesions. Studies have already shown that MRI examination is superior to other examinations as a result of the soft tissue contrast enhancement [16, 17]. The method of choice in the diagnosis and classification of liver lesions is currently dynamic contrast-enhanced MRI [18 – 20]. The liver-specific contrast agent Gd-EOB-DTPA is suitable for detecting and characterizing liver lesions particularly by combining vascular phases with an additional hepatobiliary phase [21 – 24].

The hepatobiliary phase of Gd-EOB-DTPA is made possible by the selective uptake of membrane-bound organic anion transporters (OATP1 B1 / B3) [1, 25, 26]. In addition to biliary elimination [11, 27], Gd-EOB-DTPA is also eliminated with the help of glomerular filtration in the kidneys [4]. The systems can replace one another in the event of damage to one system [28, 29].

It was already shown in different studies that liver function affects the hepatobiliary system [8 – 13]. The goal of this study was to analyze clinical factors that could influence the uptake of Gd-EOB-DTPA in a patient collective without liver parenchyma damage.

Like every human organ, the liver is subject to an aging process. In addition to a reduction in liver perfusion and liver volume, the enzyme activity of the liver decreases with age. These changes can affect the uptake as well as the elimination of metabolites [30]. The univariate analysis accordingly showed a significant negative correlation ($p = 0.021$) between patient age and signal behavior.

The transaminases AST, ALT, and GGT are located in different cell organelles. AST is primarily located in the mitochondria (80 %) but is also found free in the cytoplasm in 20 % of cases. AST is present in different organs such as the liver, heart, and skeletal musculature. Increases in AST occur primarily in the presence of liver metastases, myocarditis, pulmonary embolisms, and chronic alcohol abuse. Although there was a significant negative correlation between AST

and RE in the simple and multiple regression analysis, there was only a significant difference (p = 0.038) in the group analysis between the subgroups HRE and LRE (**Fig. 1 d**).

In contrast to AST, ALT is largely specific for liver diseases. It is free in the cytoplasm of the hepatocytes in up to 85 % of cases and is bound in the mitochondria in up to 15 % of cases. Increases in ALT are present in liver metastases and chronic alcohol abuse as well as in the case of a fatty liver. Contrary to the expected negative correlation, ALT showed a positive correlation in our collective. This paradoxical correlation with a low level of significance of p = 0.043 in the simple regression analysis did not yield significant differences between the individual subgroups in the pairwise group analysis.

In contrast to the other liver parameters, GGT is only membrane-bound. It is the most sensitive indicator in problems involving the bile duct system and the liver parenchyma. Significantly higher values were seen in the group analysis in the comparison of the LRE to the HRE (p = 0.021) and in the comparison to the MRE (p = 0032). However, significance could not be found in the multiple linear regression. Increases are seen even in the case of minor damage, such as uncomplicated viral hepatitis, mononucleosis, chronic alcohol abuse, and a fatty liver.

It was shown in recently published studies that the variance in liver volume in patients with liver cirrhosis or acute liver failure correlates well with liver function [31, 32]. Spleen size also plays an important role in the determination of liver function. Different approaches already described, such as spleen volume and the spleen/liver volume ratio, correlate with the liver fibrosis stage [33, 34]. However, different factors such as venous reflux or disruptions in the hematological system affect spleen volume. Moreover, spleen volume cannot be determined in patients with a splenectomy.

The influence of liver and spleen volume on the uptake of Gd-EOB-DTPA could only be shown in this study in the comparison of the LRE subgroup to the MRE and HRE subgroups. There was no significant difference between the MRE and HRE subgroups.

The Δ liver volume showed a significant correlation with the signal intensity change both in the regression analyses and in the pairwise group analysis.

The determination of the Δ liver volume made it possible to detect patients with a liver that is disproportionately large with respect to body weight. Since Gd-EOB-DTPA dose is determined based solely on body weight, inadequate contrast enhancement can occur in patients whose liver volume does not correlate with their body weight. Consequently, these patients receive a dose of Gd-EOB-DTPA that is too low for their liver volume thus resulting in a lower signal intensity in the HBP [3, 4]. This increases the risk of overlooking lesions in the liver parenchyma.

Liver volume-adapted administration of Gd-EOB-DTPA as a form of personalized medicine could help to increase the signal change within the liver during the HBP in these patients. Preliminary imaging can be indicative here and provide information and orientation regarding liver volume or the last contrast agent application. Insufficient doses in the preliminary examination should not be adopted. If no preliminary examinations are available, an estimation of liver volume based on unenhanced sequences prior to contrast agent administration would be a further option for adapting the quantity of Gd-EOB-DTPA to be applied.

The retrospective character of this study represents a limitation. Since this evaluation was performed retrospectively, volume-adapted administration of Gd-EOB-DTPA could not be examined. As a result, a recommendation regarding the extent of dose adaptation cannot be made on the basis of the present data. Additional studies are needed to better evaluate this data.

However, it can be concluded from the present data of this study that a weight-adapted dose of Gd-EOB-DTPA (0.1 ml/kg body weight) achieved an adequate signal change of the liver in the HBP in 93 % of patients (HRE + MRE; 115/124). Significantly limited contrast enhancement of the liver in the HBP occurred in only 7 % of the study collective (n = 9, LRE).

Clinical relevance of the study

- The liver-specific contrast agent Gd-EOB-DTPA is a widely available and widely used contrast agent in MRI liver imaging and plays a decisive role in the detection and characterization of focal as well as diffuse liver lesions.
- Less contrast enhancement of the liver in the hepatobiliary phase after 20 minutes makes it difficult to adequately diagnose liver lesions.
- It could be shown in this study that a liver volume that does not correlate to the body weight can cause an inadequate signal change after 20 minutes.

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