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CONTRAST MEDIA

Serum albumin, total bilirubin, and patient age are independent confounders of hepatobiliary-phase gadoxetate parenchymal liver enhancement

Simon Matoori[1,2] · Johannes M. Froehlich[1,2] · Stefan Breitenstein[3,4,5] · Viktoria Pozdniakova[6] · Carolin Reischauer[1] · Orpheus Kolokythas[7] · Dow-Mu Koh[8] · Andreas Gutzeit[1,2,5,8,9]

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Abstract

Purpose To identify independent confounding variables of gadoxetate-enhanced hepatobiliary-phase liver MRI using multiple regression analysis.

Materials and methods The institutional review board generally approved retrospective analyses and all patients provided written informed consent. One hundred ten patients who underwent a standardized 3.0-T gadoxetate-enhanced liver MRI between November 2008 and June 2013 were retrospectively reviewed. The gadoxetate liver enhancement normalized to enhancement in the erector spinae muscle (relative signal enhancement, SE) was related to biochemical laboratory parameters and descriptive patient characteristics (patient age, body mass index) using non-parametric univariate correlation analysis followed by a multiple linear regression model.

Results Using univariate statistics, relative SE was inversely correlated with patient age, ALP, AST, total bilirubin, gamma-glutamyltransferase, INR, model of end-stage liver disease score, and proportionally with albumin and hemoglobin (all $p < 0.01$). In a multiple regression analysis, total bilirubin ($p = 0.001$), serum albumin ($p = 0.016$), and patient age ($p = 0.018$) were independently correlated with relative liver SE ($n = 110$).

Conclusion A multiple regression analysis showed that high total bilirubin, low serum albumin, or advanced age was associated with low hepatobiliary-phase gadoxetate parenchymal liver enhancement. In these patients, the lower contrast-to-noise ratio might impair diagnostic evaluation of non-enhancing liver lesions (e.g., HCC, liver metastasis).

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✉ Simon Matoori
smatoori@ethz.ch; simon.matoori@zoho.com

✉ Andreas Gutzeit
andreas.gutzeit@hirslanden.ch

[1] Clinical Research Group, Hirslanden Clinic St. Anna, St. Anna-Strasse 32, 6006 Lucerne, Switzerland

[2] Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETH Zurich, Vladimir-Prelog-Weg 1-5 / 10, 8093 Zurich, Switzerland

[3] Department of Surgery, Clinic for Visceral and Thoracic Surgery, Cantonal Hospital Winterthur, Winterthur, Switzerland

[4] Department of Surgery, Swiss HPB (Hepato-Pancreato-Biliary) Center, University Hospital of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland

[5] Department of Radiology, Cantonal Hospital Winterthur, Winterthur, Switzerland

[6] Stavanger University Hospital, Gerd-Ragna Bloch Thorsens gate 8, 4011 Stavanger, Norway

[7] Department of Radiology, University of Washington Medical Center, Seattle, WA, USA

[8] Department of Radiology, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, England

[9] Department of Radiology, University Hospital Salzburg, Muellner Hauptstraße 48, 5020 Salzburg, Austria

Key Points

- *A multiple regression analysis identified independent confounding variables of hepatobiliary-phase gadoxetate liver enhancement.*
- *High bilirubin, low albumin, or advanced age was associated with low enhancement.*
- *Diagnostic evaluation might be hampered in these patients.*

Keywords Magnetic resonance imaging · Liver · Bilirubin · Serum albumin · Hepatobiliary agents

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BMI	Body mass index
CP	Child-Pugh
CRP	c-Reactive protein
FNH	Focal nodular hyperplasia
gGT	gamma-Glutamyltransferase
HCC	Hepatocellular carcinoma
INR	International normalized ratio
LDH	Lactate dehydrogenase
MELD	Model of end-stage liver disease
MRI	Magnetic resonance imaging
MRP2	Multidrug resistance-associated protein 2
OATP	Organic anion transporting polypeptide
ROI	Region of interest
SE	Signal enhancement

Introduction

Gadoxetate disodium (Gd-EOB-DTPA, Primovist®, Eovist®, Bayer HealthCare Pharmaceuticals) is an intravenous liver-specific magnetic resonance imaging (MRI) contrast agent [1, 2]. After the administration of the contrast agent, gadoxetate diffuses from the vascular system into the extracellular space, and approx. 50% of the dose is actively taken up into hepatocytes by at least three organic anion transporting polypeptides (OATP1A1, OATP1B1, OATP1B3) [2, 3]. Ten to 20 min after administration, in the so-called late or hepatobiliary phase, gadoxetate is actively secreted by the multidrug resistance-associated protein 2 (MRP2) into biliary canaliculi [1, 2].

The development of gadoxetate and other liver-specific contrast agents aimed at improving the contrast-to-noise ratio between hepatic lesions and the liver parenchyma. Lesions without or with aberrant hepatocytes (e.g., metastases, hepatocellular carcinoma (HCC)) do not actively take up gadoxetate and appear as non-enhancing foci against the hyperintense liver parenchyma in the hepatobiliary phase [1]. Therefore, gadoxetate is widely used to detect and characterize focal hepatic lesions (HCC, liver metastases, focal nodular hyperplasia), mainly using the hepatobiliary phase [1].

Recently, several studies reported correlations of gadoxetate liver enhancement and clinical laboratory parameters on liver function and bile formation and flow [4–11]. However, these studies were conducted with small populations, restricted sets of parameters, and/or limited to univariate statistics. Based on these correlations, the parenchymal gadoxetate liver enhancement is influenced by a variety of pathophysiological processes of the hepatobiliary system (changes in the hepatic architecture and/or loss of hepatocytes due to fibrosis, cirrhosis, or steatosis; Fig. 1) [12–16]. This finding is reflected in the current Food and Drug Administration-approved prescribing information of Eovist®. It states that reduced hepatic contrast enhancement was observed in patients with abnormally high serum bilirubin levels on gadoxetate-enhanced liver MRI, recommending that MR imaging be performed not later than 60 min after contrast injection [17]. Importantly, hepatobiliary-phase gadoxetate enhancement improved the identification and assessment of non-enhancing liver lesions compared with non-enhanced liver MRI [18–20]. Therefore, the diagnostic evaluation of non-enhancing liver lesions depends on a sufficient contrast-to-noise ratio (i.e., a strongly enhancing physiological liver parenchyma). To facilitate the identification of patients at risk for low gadoxetate parenchymal liver enhancement, we aimed at finding independently correlated variables of hepatobiliary-phase gadoxetate-enhanced liver MRI in a large population using a multiple regression analysis.

Methods

Study population

In this retrospective study, patients who underwent gadoxetate-enhanced liver MRI between November 1, 2008, and June 30, 2013, in a general public hospital for various indications (e.g., patients undergoing oncological follow-up for known extrahepatic tumors or patients with non-characterized hepatic lesions identified using other imaging modalities) were selected. Only patients who underwent clinical laboratory examinations within 10 days prior or after MRI examination were included. Exclusion criteria were either incomplete or non-interpretable MR charts, analysis by inadequate contrast-enhanced T1-weighted 3D spoiled gradient echo sequence (THRIVE), diverging MR sequences used for pre- and post-contrast imaging, or patients with previous liver resection.

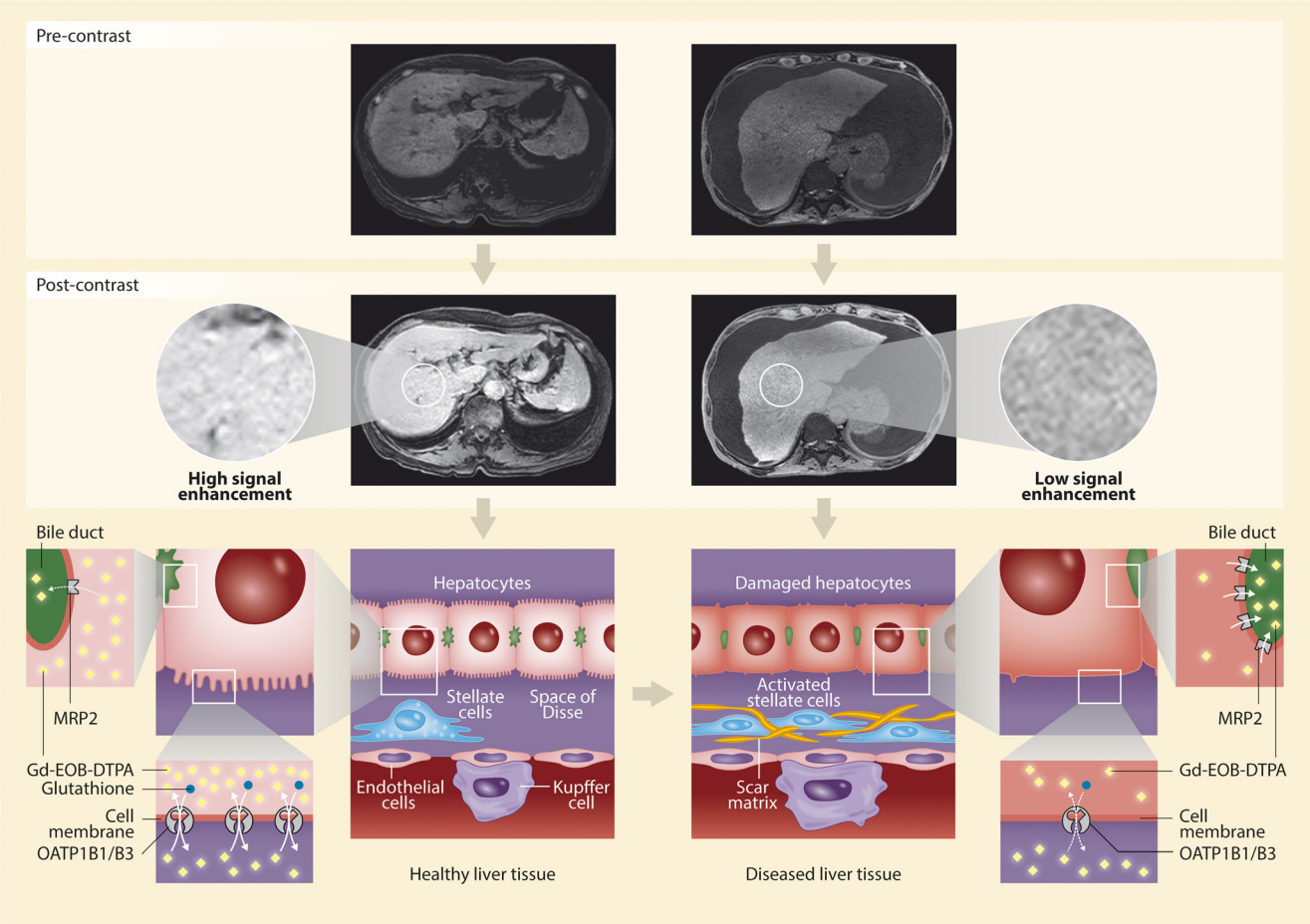

Fig. 1 T1-weighted DIXON water-enhanced MR images of a patient with low and another patient with a high signal enhancement in the hepatobiliary phase of gadoxetate-enhanced liver MRI. Schematic diagram shows key features of contrast agent kinetics in the hepatobiliary phase: vascular gadoxetate (Gd-EOB-DTPA) is actively taken up into hepatocytes by OATP1B1/B3 transporter proteins and actively secreted by MRP2 transporters into biliary canaliculi. Reduced relative signal enhancement was identified in patients with increased bilirubin ($p = 0.001$), decreased serum albumin ($p = 0.016$), or advanced age ($p = 0.018$)

General approval was given by the local ethics committee for retrospective studies. All patients had given written informed consent for retrospective data evaluation. A study based on the subpopulation of the cohort investigated here was recently published [21] but the methodology, scope, and conclusions differ significantly from this manuscript.

MR imaging

MR data were obtained on a 3.0-T scanner (Achieva, Philips Healthcare) using a standardized departmental protocol. A 16-channel surface torso coil (Philips Healthcare) covering the whole abdomen was used with the patients in supine position. Patients were scanned with breath-hold axial turbo-field-echo T1-weighted imaging, followed by a breath-hold axial T1-weighted 3D spoiled fast gradient echo sequence ("water-only"-enhanced 3D DIXON sequence, repetition time 3.3 ms, echo time 2 ms, field of view 375 mm, acquisition voxel size 1.49 mm × 1.50 mm × 3.00 mm, flip angle 10°, acquisition time 18.0 ms, intersection gap 1.5 mm). After pre-contrast acquisitions, each patient received a body weight-adjusted intravenous bolus injection of a standard dose of gadoxetate (0.025 mmol/kg body weight; injection rate 2 mL/s, Bayer HealthCare and Medtron Accutron MR), followed by a 20-mL saline flush at the same rate. Post-contrast axial T1-weighted breath-hold images (3D DIXON sequence) were obtained at 20 min after the contrast administration, corresponding to the hepatobiliary phase.

Quantitative image analysis

Image analysis was performed by three abdominal imaging experts in consensus (VP, AG, JMF, 3, 13, and 15 years of experience, respectively) who were blinded to patients' history and clinical laboratory parameters. The MR images were subsequently transferred to a PACS (Agfa) workstation. The mean parenchymal liver signal intensity (SI) was measured both on the pre-contrast and delayed hepatobiliary phase T1-

weighted images. The mean parenchymal liver SI was measured separately three times in each of the three predefined liver segments (segments VI, III, and IVB) to obtain a mean SI for each sequence (SI_{mean}). To avoid heart and breathing artifacts close to the diaphragm, we chose the segments mentioned above. A circular region of interest (ROI) with a standardized size, approximately 100 mm^2, was placed within the same anatomical location for each sequence. Vessels, biliary structures, and prominent artifacts were carefully avoided. The mean SI of the right erector spinae muscle was also measured by placing a similarly sized ROI approximately on the same image section as that of the hepatic parenchymal SI measurements. Muscular enhancement was measured pre- and post-contrast in order to normalize shimming influences and correct for eventual technical bias by using the muscle as a reference on the same plane [22, 23]. We therefore defined the adjustment factor F:

$$F = SI_{\text{muscle pre}}/SI_{\text{muscle post}}$$

The relative SE at 20 min was calculated using the following equation:

$$\text{Relative SE} = \left(F \times SI_{\text{liver post}}\right)/SI_{\text{liver pre}}$$

Clinical laboratory parameters

Serum biochemical laboratory parameters obtained within 10 days to the MRI study were extracted from the hospital's RIS (Radiology Information System). The following parameters were included in the analysis: thrombocyte count, total bilirubin, AST, alanine transaminase (ALT), ALP, gGT, albumin, lactate dehydrogenase (LDH), hemoglobin, serum creatinine, and the international normalized ratio. The body mass index (BMI), the model of end-stage liver disease (MELD) score, and the Child-Pugh score were calculated [24]. To determine the Child-Pugh score, a clinical assessment with regard to the presence of ascites and hepatic encephalopathy was additionally carried out [24].

Evaluation and statistical analysis

Analyses were performed using SPSS version 20 (IBM), R version 3.1.1 (R Foundation for Statistical Computing), or SigmaPlot 13.0 (Systat Software).

Non-parametric univariate correlation analysis (Spearman's rank-order correlation) was performed for relative SE and the following parameters: thrombocyte count, INR, total bilirubin, AST, ALT, ALP, gGT, albumin, creatinine, LDH, BMI, MELD score. A p value < 0.05 was deemed statistically significant. The univariate correlation analyses have an explorative character and are not controlled for multiple tests.

The following nine variables were considered for a linear regression model with the dependent variable relative SE: patient age, albumin, ALP, AST, total bilirubin, gGT, INR, MELD score, and hemoglobin. Correlations between independent variable analyses were carried out and variables which correlated with $r > 0.70$ (AST) were excluded (supplementary Figure S1). Bilirubin, AST, INR, alkaline phosphatase, MELD score, and gGT were log-transformed, and for hemoglobin, one extreme outlier with a value of 44 was deleted. However, as some of those variables had a large proportion of missing data (Table 2), a multiple imputation followed by a linear regression was performed. For the imputation model, all variables from the full model were included. In addition, variables with an absolute correlation with the target variables of at least 0.3 and with a proportion of usable cases (cases with missing data on the target variable that had observed values on the predictor) of at least 30% were retained in the imputation model. Depending on the scale of the target variable, multiple imputation was performed using either predictive mean matching (pmm) or logistic regression (logreg). One hundred imputed data sets were generated. Imputation was assessed via density plots for plausibility, i.e., whether imputed data were possible and close to the observed data. For predictor selection of the multiple linear regression, the Wald function was used to test whether variables show a relationship among the data items in the final model. The final model included age, albumin, and bilirubin. Interaction was tested for these variables.

Subgroup analysis for cirrhotic and non-cirrhotic patients

The analyses were performed in the R programming language (version 3.3.3) (R Core Team 2017). The package "mice" (Buuren and Groothuis-Oudshoorn 2011) was used to perform the multiple imputation.

To assess the influence of liver cirrhosis on relative liver SE, the statistical analyses described above were performed for patients with and without known cirrhosis.

The comparison of patient groups with different CP scores (Fig. 2d) was carried out with a one-way analysis of variance (ANOVA). Both the normality test (Shapiro-Wilk) and the equal variance test (Brown-Forsythe) were passed ($p = 0.867$ and $p = 0.072$, respectively).

For patients with no cirrhosis, a linear regression model was performed. Fourteen variables were considered as independent predictors (age, albumin, alkaline phosphatase, AST, total bilirubin, gGT, INR, MELD score, hemoglobin, ALT, BMI, creatinine, thrombocytes, c-reactive protein (CRP)). However, as there were only 76 patients without cirrhosis, we planned a model with no more than seven predictors. LDH (18/76) and albumin (25/76) had few valid cases and were therefore not considered for the linear regression model. BMI, creatinine, and thrombocytes did not seem to be

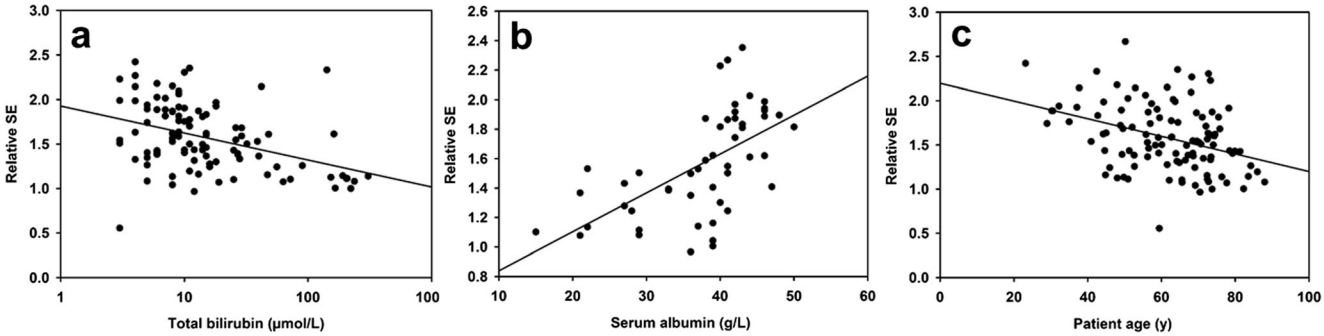

Fig. 2 Scatterplots with linear regression line showing relative SE on gadoxetate-enhanced hepatobiliary phase liver MRI versus patient age (**a**, $n = 110$), serum albumin (**b**, $n = 50$), and total bilirubin (**c**, $n = 101$). In a multiple regression analysis, total bilirubin ($p = 0.001$), serum albumin ($p = 0.016$), and patient age ($p = 0.018$, **a**–**c**) were identified as independently correlated variables of relative hepatobiliary-phase gadoxetate parenchymal liver SE. Decreased gadoxetate liver enhancement was therefore observed in patients with reduced serum albumin, increased total bilirubin, and advanced age. Potentially, the reduced hepatobiliary-phase signal enhancement in the liver parenchyma of these patients may hamper diagnostic evaluation of non-enhancing liver lesions due to a lower contrast-to-noise ratio

correlated with signal intensity and were therefore not included in the linear regression model. Correlation analysis (see above) led to the exclusion of ALT, MELD score, and alkaline phosphatase from the linear regression model (supplementary Figure S2). Bilirubin, AST, INR, alkaline phosphatase, gGT, and CRP were natural log-transformed.

As the proportion of complete cases was only 59% of all data, a multiple imputation was performed with 100 imputed data sets. For the imputation model, all variables with an absolute correlation with the target variables of at least 0.3 and with a proportion of usable cases (cases with missing data on the target variable that had observed values on the predictor) of at least 30% were retained in the imputation model. Serum albumin was not included in the multiple regression analysis due to the high amount of missing values (63%).

A linear regression was performed with change in signal intensity as the dependent variable and the following independent variables: age, AST, total bilirubin, gGT, INR, hemoglobin, and CRP.

Results

Study population

A cohort of 144 patients with diverse clinical backgrounds, who had undergone gadoxetate-enhanced MRI and whose clinical laboratory parameters were evaluated, was further assessed for eligibility. Patients were excluded due to incomplete charts ($n = 13$), different MR sequences used for pre- and post-contrast MR imaging ($n = 6$), imaging performed using other T1-weighted sequences ($n = 13$) than the one described above, non-interpretable MR examination ($n = 1$), or previous liver resection ($n = 1$). Finally, a cohort of 110 patients (Table 1) was included in the study.

Correlations of relative SE with biochemical laboratory parameters

Based on univariate statistical analysis in all patients, relative liver SE was significantly inversely correlated with patient age (rho = − 0.350; $p < 0.001$, $n = 110$), AST (rho = − 0.251; $p = 0.007$, $n = 101$), gGT (rho = − 0.377; $p < 0.001$, $n = 73$), total bilirubin (rho = − 0.405; $p < 0.001$, $n = 101$), INR (rho = − 0.359, $p < 0.001$, $n = 83$), MELD score (rho = − 0.414; $p < 0.001$, $n = 71$), CRP (rho = − 0.301, $p < 0.001$, $n = 100$), and alkaline phosphatase (rho = − 0.382; $p < 0.001$, $n = 96$),

Table 1 Summary of patient characteristics

Total number of patients	$n = 110$
Female patients	$n = 43$ (39.1%)
Male patients	$n = 67$ (60.9%)
Mean age (min, max), years	61.5 (23.1, 88.0)
Mean BMI (min, max), kg/m^2	25.6 (16.8, 41.7)
Mean relative hepatobiliary-phase liver SE (min, max)	1.59 (0.56, 2.67)
Patients without cirrhosis	$n = 76$ (69.1%)
Patients with cirrhosis	$n = 34$ (30.9%)
Child-Pugh score (in cirrhotic patients)	
A	$n = 20$ (18.2%)
B	$n = 7$ (6.4%)
C	$n = 4$ (3.6%)
Unclassified	$n = 3$ (2.7%)
Patients with liver metastasis	$n = 29$ (26.4%)
Patients with primary liver tumors/lesions	$n = 21$ (19.1%)
HCC	$n = 10$
Suspected HCC	$n = 3$
Cholangiocarcinoma	$n = 7$
Focal nodular hyperplasia (FNH)	$n = 1$
Patients without primary liver tumor	$n = 89$ (80.9%)

and positively correlated with serum albumin (rho = 0.690; $p < 0.001$, $n = 50$) and hemoglobin (rho = 0.317; $p < 0.001$, $n = 109$). No correlations were identified between relative SE and ALT ($p = 0.432$, $n = 100$), BMI ($p = 0.555$, $n = 84$), creatinine ($p = 0.702$, $n = 99$), LDH ($p = 0.680$, $n = 22$), and thrombocyte count ($p = 0.585$, $n = 108$) (Table 2).

In a multiple regression analysis ($n = 110$), relative SE was significantly inversely correlated with patient age ($p = 0.018$) and total bilirubin ($p = 0.001$) and positively with serum albumin ($p = 0.016$) (Table 3). Therefore, decreased gadoxetate enhancement of the liver was independently associated with increased patient age, increased total bilirubin, and decreased serum albumin. Interaction analysis confirmed that these three variables did not interact. No such significant association was found in the multiple regression analysis for the other determined parameters (ALP, AST, gGT, hemoglobin, INR, MELD score) despite yielding significant correlations with relative SE in the univariate analyses.

Subgroup analysis for cirrhotic and non-cirrhotic patients

A univariate analysis in patients without known cirrhosis yielded significant negative correlations of patient age (rho = − 0.500; $p < 0.001$, $n = 76$), ALP (rho = − 0.384; $p = 0.001$, $n = 67$), AST (rho = − 0.237; $p = 0.048$, $n = 70$), gGT (rho = − 0.356; $p = 0.010$, $n = 51$), INR (rho = − 0.324; $p = 0.018$, $n = 53$), MELD score (rho = − 0.411; $p = 0.006$, $n = 43$), and total bilirubin (rho = − 0.385; $p = 0.001$, $n = 68$) with relative gadoxetate liver SE. Significant positive correlations with relative SE were observed for serum albumin (rho = 0.593; $p = 0.002$, $n = 25$) and hemoglobin (rho = 0.255; $p = 0.028$, $n = 74$) (Table 4).

A multiple regression analysis ($n = 76$) in non-cirrhotic patients showed that patient age ($p = 0.002$) was the only significant predictor with bilirubin trending towards significance ($p = 0.053$). Of note, serum albumin was not included in the multiple regression analysis due to the high percentage of missing values (67%) (Table 5).

A univariate analysis in patients with known cirrhosis showed that AST (rho = − 0.477; $p = 0.007$, $n = 31$), CRP (rho = − 0.580; $p = 0.001$, $n = 29$), and total bilirubin (rho = − 0.363; $p = 0.038$, $n = 33$) are significantly negatively correlated with relative gadoxetate SE. Significant positive correlations with relative SE were found for serum albumin (rho = 0.709; $p < 0.001$, $n = 25$) and hemoglobin (rho = 0.442; $p = 0.009$, $n = 34$) (Table 6). A multiple regression analysis was not carried out due to the low number of patients.

Relating the relative gadoxetate SE with the Child-Pugh score showed a trend towards lower enhancement with more advanced liver cirrhosis ($p = 0.064$; Fig. 3).

Discussion

The main result of this multiple regression analysis was that total bilirubin ($p = 0.001$), serum albumin ($p = 0.016$), and patient age ($p = 0.018$) were independently correlated with relative gadoxetate liver SE in the hepatobiliary phase. Therefore, patients with decreased serum albumin, or increased total bilirubin, or advanced age showed reduced gadoxetate enhancement of the liver parenchyma. The diagnostic evaluation may be hampered in patients with reduced liver enhancement due to a lower contrast-to-noise ratio.

Table 2 Univariate analysis of the correlation of relative liver gadoxetate SE in the hepatobiliary phase and patient characteristics, clinical laboratory parameters, and MELD score (*$p < 0.05$, Spearman's rank-order correlation)

Parameter	Median (min, max)	Spearman's coefficient (rho)	p value
Patient age (years)	63.8 (23.1, 88.0)	− 0.350	$p < 0.001$ ($n = 110$)*
BMI (kg/m^2)	24.7 (16.8, 41.7)	0.065	$p = 0.555$ ($n = 84$)
ALP (U/L)	104 (13, 1790)	− 0.404	$p < 0.001$ ($n = 96$)*
ALT (U/L)	48 (8, 1956)	− 0.079	$p = 0.432$ ($n = 100$)
AST (U/L)	47 (13, 1625)	− 0.298	$p = 0.002$ ($n = 101$)*
CRP (mg/L)	13 (3, 642)	− 0.301	$p < 0.001$ ($n = 100$)*
Creatinine (μmol/L)	71 (35, 425)	0.039	$p = 0.702$ ($n = 99$)
gGT (U/L)	168 (15, 1858)	− 0.392	$p < 0.001$ ($n = 73$)*
Hemoglobin (g/dL)	13.0 (6.2, 44.0)	0.317	$p < 0.001$ ($n = 109$)*
INR	1.15 (0.92, 3.80)	− 0.359	$p < 0.001$ ($n = 83$)*
LDH (U/L)	385 (55, 612)	− 0.093	$p = 0.680$ ($n = 22$)
MELD score	8.7 (6.0, 30.0)	− 0.414	$p < 0.001$ ($n = 71$)*
Serum albumin (g/L)	40 (15, 50)	0.690	$p < 0.001$ ($n = 50$)*
Thrombocyte count (×10^9/L)	231 (34, 846)	0.053	$p = 0.585$ ($n = 108$)
Total bilirubin (μmol/L)	11 (3, 306)	− 0.414	$p < 0.001$ ($n = 101$)*

Table 3 Multiple linear regression of gadoxetate relative liver SE in the hepatobiliary phase (estimate, standard error (SE), and 95% confidence interval (CI), *p* value (* < 0.05), *n* = 110; missing values were determined by multiple imputation)

Predictors	Estimate	SE	95% CI	*p* value
Patient age	− 0.004	0.002	− 0.007 to − 0.001	0.018*
Serum albumin	0.012	0.005	0.002–0.022	0.016*
Total bilirubin	− 0.239	0.07	− 0.378 to − 0.100	0.001*
Alkaline phosphatase	− 0.064	0.177	− 0.418 to 0.290	0.719
AST	0.141	0.106	− 0.069 to 0.352	0.185
gGT	− 0.066	0.117	− 0.302 to 0.169	0.572
INR	− 0.265	0.536	− 1.331 to 0.802	0.623
MELD score	− 0.257	0.408	− 1.069 to 0.556	0.531
Hemoglobin	0.013	0.017	− 0.020 to 0.046	0.433

Using univariate statistics in all patients, we observed that relative liver SE on hepatobiliary-phase gadoxetate-enhanced liver MRI was correlated with several clinical laboratory parameters (total bilirubin, serum albumin, ALP, AST, total bilirubin, gGT, albumin, hemoglobin, INR, CRP), the MELD score, and patient age (Table 2). Several retrospective studies have shown an association of biochemical laboratory parameters of the hepatobiliary system and hepatobiliary-phase gadoxetate liver enhancement [4–9, 25]. However, these studies mostly included small populations, restricted sets of clinical laboratory parameters, and lacked a multiple regression analysis to identify the independently correlated variables.

Our multiple regression analysis ($n = 110$) revealed that only albumin ($p = 0.016$), total bilirubin ($p = 0.001$), and patient age ($p = 0.018$) are independently correlated with relative liver SE (Table 3). Therefore, impaired hepatic protein synthesis (i.e., low serum albumin) [26], liver disease (e.g., hepatitis), as well as reduced hepatobiliary clearance (i.e., high total bilirubin) [26], and advanced patient age were associated with low gadoxetate liver enhancement. Importantly, hepatobiliary-phase gadoxetate liver enhancement improved the diagnostic evaluation of non-enhancing liver lesions compared with non-enhanced liver MRI [18–20]. Therefore, the identification and assessment of non-enhancing liver lesions are facilitated against a strongly enhanced liver parenchyma. Given that patients with low serum albumin, high total bilirubin, or advanced age showed low gadoxetate parenchymal enhancement, diagnostic evaluations should be conducted cautiously in these patients.

Our multiple regression analysis furthermore identified an independent inverse correlation of patient age with gadoxetate liver enhancement in the hepatobiliary phase in all patients ($p = 0.018$) and in non-cirrhotic patients ($p = 0.002$). In the literature, an association of patient age with gadoxetate liver enhancement was described in univariate statistical analyses [21, 27]. Using a multiple regression analysis, we were able to establish the independent nature of this reported association by controlling for confounding factors (e.g., hepatobiliary

Table 4 Univariate analysis for patients without known cirrhosis of the correlation of relative liver gadoxetate SE and patient characteristics, clinical laboratory parameters, and MELD score (*$p < 0.05$, Spearman's rank-order correlation)

Parameter	Spearman's rho	*p* value
Patient age (years)	− 0.500	$p < 0.001$ ($n = 76$)*
BMI (kg/m^2)	0.024	$p = 0.861$ ($n = 57$)
ALP (U/L)	− 0.384	$p = 0.001$ ($n = 67$)*
ALT (U/L)	− 0.111	$p = 0.362$ ($n = 69$)
AST (U/L)	− 0.237	$p = 0.048$ ($n = 70$)*
CRP (mg/L)	− 0.229	$p = 0.055$ ($n = 71$)
Creatinine (μmol/L)	0.030	$p = 0.807$ ($n = 69$)
gGT (U/L)	− 0.356	$p = 0.010$ ($n = 51$)*
Hemoglobin (g/dL)	0.255	$p = 0.028$ ($n = 74$)*
INR	− 0.324	$p = 0.018$ ($n = 53$)*
LDH (U/L)	− 0.276	$p = 0.268$ ($n = 18$)
MELD score	− 0.411	$p = 0.006$ ($n = 43$)*
Serum albumin (g/L)	0.593	$p = 0.002$ ($n = 25$)*
Thrombocyte count (×10^9/L)	0.007	$p = 0.952$ ($n = 74$)
Total bilirubin (μmol/L)	− 0.385	$p = 0.001$ ($n = 68$)*

Table 5 Multiple linear regression of relative SE in patients without known cirrhosis (estimate, standard error (SE), and 95% confidence interval (CI), *p* value (* < 0.05), *n* = 76; missing values were determined by multiple imputation). Serum albumin was not included in the multiple linear regression analysis due to the high percentage (67%) of missing values

Predictors	Estimate	SE	95% CI	*p* value
Patient age	− 0.010	0.003	− 0.016 to − 0.004	0.002*
AST	0.046	0.049	− 0.051 to 0.144	0.348
Total bilirubin	− 0.090	0.045	− 0.181 to 0.001	0.053
INR	− 0.288	0.224	− 0.738 to 0.162	0.205
gGT	− 0.055	0.047	− 0.149 to 0.039	0.241
Hemoglobin	0.015	0.023	− 0.031 to 0.061	0.516
CRP	0.030	0.033	− 0.035 to 0.095	0.364

Table 6 Univariate analysis for patients with known cirrhosis of the correlation of relative liver gadoxetate SE and patient characteristics, clinical laboratory parameters, and MELD score (*$p < 0.05$, Spearman's rank-order correlation)

Parameter	Spearman's rho	p value
Patient age (years)	0.136	$p = 0.443$ ($n = 34$)
BMI (kg/m^2)	0.222	$p = 0.265$ ($n = 27$)
ALP (U/L)	− 0.367	$p = 0.050$ ($n = 29$)
ALT (U/L)	− 0.126	$p = 0.498$ ($n = 31$)
AST (U/L)	− 0.477	$p = 0.007$ ($n = 31$)*
CRP (mg/L)	− 0.580	$p = 0.001$ ($n = 29$)*
Creatinine (μmol/L)	− 0.027	$p = 0.886$ ($n = 30$)
gGT (U/L)	− 0.354	$p = 0.106$ ($n = 22$)
Hemoglobin (g/dL)	0.442	$p = 0.009$ ($n = 34$)*
INR	− 0.317	$p = 0.088$ ($n = 30$)
LDH (U/L)	0.800	$p = 0.200$ ($n = 4$)
MELD score	− 0.348	$p = 0.070$ ($n = 28$)
Serum albumin (g/L)	0.709	$p < 0.001$ ($n = 25$)*
Thrombocyte count (×10^9/L)	− 0.036	$p = 0.840$ ($n = 34$)
Total bilirubin (μmol/L)	− 0.363	$p = 0.038$ ($n = 33$)*

pathologies with a bearing on clinical laboratory parameters). Age-related changes in the liver parenchyma (e.g., lower OATP1 transporter expression, fibrotic or steatotic changes, decreased perfusion rate) may account for the correlation observed in our study [28–30]. Interestingly, patient age was not a significant confounder of hepatic enhancement in the subpopulation of cirrhotic patients ($p = 0.443$) highlighting the importance of cirrhosis-related pathological changes on gadoxetate liver enhancement in these patients [6, 31–33].

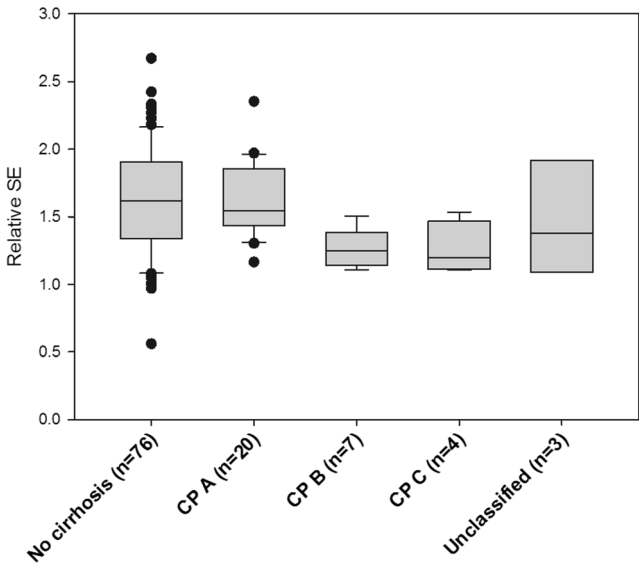

Fig. 3 Box plot showing relative gadoxetate liver SE in the hepatobiliary phase in relation to the Child-Pugh (CP) score ($n = 110$). Patients with more advanced liver cirrhosis showed a trend towards lower relative liver enhancement ($p = 0.064$)

To investigate the effect of liver cirrhosis on relative liver SE in closer detail, we conducted a univariate analysis in cirrhotic patients and observed significant associations with total bilirubin, serum albumin, AST, and CRP (Table 6). These correlations highlight the influence of pathologic changes of the hepatobiliary system and inflammation on gadoxetate liver enhancement in the hepatobiliary phase [6, 31–33]. Furthermore, a trend towards lower relative SE was observed in patients with higher Child-Pugh score ($p = 0.064$; Fig. 3), which is in accordance with the literature [6, 32].

In addition to the retrospective design, further limitations of this study have to be considered. Particularly, an influence of unidentified external factors on the laboratory parameters cannot be ruled out (e.g., medication (e.g., chemotherapy), comorbidities (e.g., chronic or low-grade hepatitis, kidney disease), nutritional status, genetic factors, or other physiological and pathophysiological influences), especially with regard to the missing control group. In the cirrhotic subpopulation, a multiple regression analysis could not be carried out due to the low number of patients. Moreover, the delay between the acquisition of the scans and the publication of the study is related to the complex and time-consuming data retrieval, quantification, and statistical analysis. The retrospective nature of this study did not allow us to include a further clinical laboratory parameter of interest, cholinesterase [34], which is not routinely measured in our institution. In addition, liver biopsy was not performed to confirm liver cirrhosis, as this invasive procedure is not routinely carried out in patients undergoing liver MRI in our hospital. We further acknowledge that the missing sensitivity analysis, which aims at testing the robustness of the method to account for the missing values, is a limitation of this study. Finally, we lack data on the diagnostic performance of the radiologists reading the gadoxetate-enhanced MRI scans of this study. Therefore, quantifying the impact of the observed decreased gadoxetate enhancement on the gadoxetate-based diagnostic liver evaluations would be beyond the scope of this manuscript. Nonetheless, poor hepatic parenchymal enhancement may in theory affect the detection of small non-hepatocellular focal liver lesions.

In conclusion, our multiple regression analysis ($n = 110$) identified serum albumin ($p = 0.016$), total bilirubin ($p = 0.001$), and patient age ($p = 0.018$) as independently correlated variables of hepatobiliary-phase gadoxetate parenchymal liver enhancement. The reduced hepatobiliary-phase gadoxetate liver enhancement in patients with decreased serum albumin, increased total bilirubin, or advanced age might complicate the diagnostic evaluation of non-enhancing liver lesions (e.g., HCC, liver metastasis). Further studies are needed to evaluate the effect of the lower contrast-to-noise ratio on diagnostic accuracy.

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Compliance with ethical standards

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

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in Matoori et al *European Radiology* 2016;26(6):1889–1894. The scope and conclusions of the present study differ significantly from the published work.

Methodology
- Retrospective
- Observational
- Performed at one institution

References

1. Van Beers BE, Pastor CM, Hussain HK (2012) Primovist, Eovist: what to expect? J Hepatol 57:421–429
2. Reimer P, Schneider G, Schima W (2004) Hepatobiliary contrast agents for contrast-enhanced MRI of the liver: properties, clinical development and applications. Eur Radiol 14:559–578
3. Giraudeau C, Leporq B, Doblas S et al (2017) Gadoxetate-enhanced MR imaging and compartmental modelling to assess hepatocyte bidirectional transport function in rats with advanced liver fibrosis. Eur Radiol 27:1804–1811
4. Higaki A, Tamada T, Sone T et al (2012) Potential clinical factors affecting hepatobiliary enhancement at Gd-EOB-DTPA-enhanced MR imaging. Magn Reson Imaging 30:689–693
5. Chen BB, Hsu CY, Yu CW et al (2014) Hepatic necro-inflammation and elevated liver enzymes: evaluation with MRI perfusion imaging with gadoxetic acid in chronic hepatitis patients. Clin Radiol 69: 473–480
6. Kukuk GM, Schaefer SG, Fimmers R et al (2014) Hepatobiliary magnetic resonance imaging in patients with liver disease: correlation of liver enhancement with biochemical liver function tests. Eur Radiol 24:2482–2490
7. Haimerl M, Verloh N, Fellner C et al (2014) MRI-based estimation of liver function: Gd-EOB-DTPA-enhanced T1 relaxometry of 3T vs. the MELD score. Sci Rep 4:5621
8. Utsunomiya T, Shimada M, Hanaoka J et al (2012) Possible utility of MRI using Gd-EOB-DTPA for estimating liver functional reserve. J Gastroenterol 47:470–476
9. Nakamura S, Awai K, Utsunomiya D et al (2012) Chronological evaluation of liver enhancement in patients with chronic liver disease at Gd-EOB-DTPA-enhanced 3-T MR imaging: does liver function correlate with enhancement? Jpn J Radiol 30:25–33
10. Chernyak V, Kim J, Rozenblit AM, Mazzoriol F, Ricci Z (2011) Hepatic enhancement during the hepatobiliary phase after gadoxetate disodium administration in patients with chronic liver disease: the role of laboratory factors. J Magn Reson Imaging 34: 301–309
11. Kobi M, Paroder V, Flusberg M, Rozenblit AM, Chernyak V (2017) Limitations of GD-EOB-DTPA-enhanced MRI: can clinical parameters predict suboptimal hepatobiliary phase? Clin Radiol 72:55–62
12. Tsuda N, Okada M, Murakami T (2007) Potential of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) for differential diagnosis of nonalcoholic steatohepatitis and fatty liver in rats using magnetic resonance imaging. Invest Radiol 42:242–247
13. Tsuda N, Matsui O (2010) Cirrhotic rat liver: reference to transporter activity and morphologic changes in bile canaliculi—gadoxetic acid–enhanced MR imaging. Radiology 256:767–773
14. Tsuda N, Matsui O (2011) Signal profile on Gd-EOB-DTPA-enhanced MR imaging in non-alcoholic steatohepatitis and liver cirrhosis induced in rats: correlation with transporter expression. Eur Radiol 21:2542–2550
15. Feier D, Balassy C, Bastati N, Stift J, Badea R, Ba-Ssalamah A (2013) Liver fibrosis: histopathologic and biochemical influences on diagnostic efficacy of hepatobiliary contrast-enhanced MR imaging in staging. Radiology 269:460–468
16. Bastati N, Feier D, Wibmer A et al (2014) Noninvasive differentiation of simple steatosis and steatohepatitis by using gadoxetic acid–enhanced MR imaging in patients with nonalcoholic fatty liver disease: a proof-of-concept study. Radiology 271:739–747
17. US Food and Drug Administration (2018) Eovist(R): highlights of prescribing information available via https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022090s015,201277s015lbl.pdf Accessed on 23 Jan 2019
18. Bieze M, van den Esschert JW, Nio CY et al (2012) Diagnostic accuracy of MRI in differentiating hepatocellular adenoma from focal nodular hyperplasia: prospective study of the additional value of gadoxetate disodium. AJR Am J Roentgenol 199:26–34
19. Bashir MR, Gupta RT, Davenport MS et al (2013) Hepatocellular carcinoma in a North American population: does hepatobiliary MR imaging with Gd-EOB-DTPA improve sensitivity and confidence for diagnosis? J Magn Reson Imaging 37:398–406
20. Ahn SS, Kim MJ, Lim JS, Hong HS, Chung YE, Choi JY (2010) Added value of gadoxetic acid–enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology 255:459–466
21. Matoori S, Froehlich JM, Breitenstein S et al (2016) Age dependence of spleen- and muscle-corrected hepatic signal enhancement on hepatobiliary phase gadoxetate MRI. Eur Radiol 26:1889–1894
22. Katsube T, Okada M, Kumano S et al (2012) Estimation of liver function using T2* mapping on gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging. Eur J Radiol 81:1460–1464
23. Nishie A, Ushijima Y, Tajima T et al (2012) Quantitative analysis of liver function using superparamagnetic iron oxide- and Gd-EOB-DTPA-enhanced MRI: comparison with technetium-99m galactosyl serum albumin scintigraphy. Eur J Radiol 81:1100–1104
24. Wiesner R, Edwards E, Freeman R et al (2003) Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 124:91–96
25. Verloh N, Haimerl M, Zeman F et al (2015) Multivariable analysis of clinical influence factors on liver enhancement of Gd-EOB-DTPA-enhanced 3T MRI. Rofo 187:29–35

26. Neuschwander-Tetri BA, Clark JM, Bass NM et al (2010) Clinical, laboratory and histological associations in adults with nonalcoholic fatty liver disease. Hepatology 52:913–924
27. Geisel D, Raabe P, Lüdemann L et al (2017) Gd-EOB-DTPA-enhanced MRI for monitoring future liver remnant function after portal vein embolization and extended hemihepatectomy: a prospective trial. Eur Radiol 27:3080–3087
28. Mooij MG, Schwarz UI, de Koning BAE et al (2014) Ontogeny of human hepatic and intestinal transporter gene expression during childhood: age matters. Drug Metab Dispos 42:1268–1274
29. Dowman JK, Tomlinson JW, Newsome PN (2011) Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Aliment Pharmacol Ther 33:525–540
30. Georgiou L, Penny J, Nicholls G et al (2017) Quantitative assessment of liver function using gadoxetate-enhanced magnetic resonance imaging: monitoring transporter-mediated processes in healthy volunteers. Invest Radiol 52:111–119
31. Ahmed BS, Nina B, Andreas W et al (2017) Hepatic gadoxetic acid uptake as a measure of diffuse liver disease: where are we? J Magn Reson Imaging 45:646–659
32. Nilsson H, Blomqvist L, Douglas L, Nordell A, Jonas E (2010) Assessment of liver function in primary biliary cirrhosis using Gd-EOB-DTPA-enhanced liver MRI. HPB (Oxford) 12:567–576
33. Nilsson H, Blomqvist L, Douglas L et al (2013) Gd-EOB-DTPA-enhanced MRI for the assessment of liver function and volume in liver cirrhosis. Br J Radiol 86:20120653
34. Hinrichs H, Hinrichs JB, Gutberlet M et al (2016) Functional gadoxetate disodium-enhanced MRI in patients with primary sclerosing cholangitis (PSC). Eur Radiol 26:1116–1124

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