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Hepatobiliary phase in cirrhotic patients with different Model for End-stage Liver Disease score: comparison of the performance of gadoxetic acid to gadobenate dimeglumine

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Abstract

Objectives The purpose of this study was to compare the performance of gadobenate dimeglumine–enhanced MRI and gadoxetic acid–enhanced MRI in the hepatobiliary phase (HBP) in cirrhotic patients with different degrees of liver dysfunction.

Methods In this retrospective cross-sectional study, we analyzed the unenhanced phase and the HBP of 131 gadobenate dimeglumine–enhanced MRI examinations (gadobenate dimeglumine group) and 127 gadoxetic acid–enhanced MRI examinations (gadoxetic acid group) performed in 249 cirrhotic patients (181 men and 68 women; mean age, 64.8 years) from August 2011 to April 2017. For each MRI, the contrast enhancement index of the liver parenchyma was calculated and correlated to the Model For End-Stage Liver Disease (MELD) score (multiple linear regression analysis). A qualitative analysis of the adequacy of the HBP, adjusted for the MELD score (logistic regression analysis), was performed.

Results The contrast enhancement index was inversely related ($r = -0.013$) with MELD score in both gadoxetic acid and gadobenate dimeglumine group. At the same MELD score, the contrast enhancement index in the gadoxetic acid group was increased by a factor of 0.23 compared to the gadobenate dimeglumine group ($p < 0.001$), and the mean odds ratio to have an adequate HBP with gadoxetic acid compared to gadobenate dimeglumine was 3.64 ($p < 0.001$). The adequacy of the HBP in the gadoxetic acid group compared to the gadobenate dimeglumine group increased with the increase of the MELD score (exp(b)interaction = 1.233; $p = 0.011$).

Conclusion In cirrhotic patients, the hepatobiliary phase obtained with gadoxetic acid–enhanced MRI is of better quality in comparison to gadobenate dimeglumine–enhanced MRI, mainly in patients with high MELD score.

Key Points

- *In cirrhotic patients, the adequacy of the hepatobiliary phase with gadoxetic acid–enhanced MRI is better compared to gadobenate dimeglumine–enhanced MRI.*
- *Gadoxetic acid–enhanced MRI should be preferred to gadobenate dimeglumine–enhanced MRI in cirrhotic patients with MELD score > 10, if the hepatobiliary phase is clinically indicated.*
- *In patients with high MELD score (> 15), the administration of the hepatobiliary agent could be useless; even though, if it is clinically indicated, we recommend to use gadoxetic acid given the higher probability of obtaining clinically relevant information.*

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Keywords Liver cirrhosis · Gadolinium ethoxybenzyl DTPA · Gadobenic acid · Magnetic resonance imaging

Abbreviations

CEI	Contrast enhancement index
HBP	Hepatobiliary phase
MELD	Model for end-stage liver disease
MRI	Magnetic resonance imaging
SIR	Signal intensity ratio

Introduction

Hepatobiliary gadolinium–based contrast agents, including gadobenate dimeglumine and gadoxetic acid, have the dual properties for dynamic and hepatobiliary imaging. They are actively transported into functioning hepatocytes and subsequently excreted into the bile. Important differences in hepatocellular uptake of these agents (50% with gadoxetic acid and 3–5% with gadobenate dimeglumine) [1] lead to agent-specific enhancement patterns that can yield improved detection and characterization of lesions. Though this difference in hepatocellular uptake, similar hepatic parenchymal enhancement in the hepatobiliary phase (HBP) obtained with these two agents was observed in healthy volunteers [2, 3].

In cirrhotic patients, the distortion of hepatic architecture is associated with a reduction in the number of functioning hepatocytes and an impaired biliary excretion [4]. This explains the decreased liver enhancement in the HBP in cirrhotic patients, which may ultimately result in an inadequate HBP that compromises lesion detection and characterization [5–13]. We postulate that in cirrhotic patients, the lower percentage of hepatocytes uptake of gadobenate dimeglumine compared to gadoxetic acid may result into a higher probability of inadequate HBP with gadobenate dimeglumine. Identification of patients with a high likelihood of an inadequate HBP can help in the choice of the best hepatobiliary contrast agent. This would ultimately result in better detection and characterization of focal liver lesions as well as estimation of liver function. However, no previous studies demonstrated whether there is any difference between gadobenate dimeglumine–enhanced MRI and gadoxetic acid–enhanced MRI in obtaining an adequate HBP in patients with compensated cirrhosis as opposed to patients with more advanced disease.

The purpose of this study was to compare the performance of gadobenate dimeglumine–enhanced MRI and gadoxetic acid–enhanced MRI in the HBP in cirrhotic patients with different degrees of liver dysfunction.

Materials and methods

This retrospective cross-sectional bicentric study was approved by the Institutional Review Boards of University of Milan and University of Palermo, referral centers for liver diseases, and a waiver of informed consent was obtained.

Study cohort

Figure 1 portrays the subjects' accrual flowchart [14]. In each center, we retrospectively searched the departmental electronic database for consecutive patients who had liver MRI between August 2011 and April 2017. Patients were eligible for inclusion if they had liver MRI with gadobenate dimeglumine (MultiHance, Bracco Imaging S.p.A.) in the University of Milan and with gadoxetic acid (Primovist, Bayer AG) in the University of Palermo and if "cirrhosis" was the clinical indication. Subjects were considered ineligible for this study if (a) patients had previous hepatic or biliary surgery or transarterial or ablation therapies for hepatic lesions, (b) clinical data were incomplete, and (c) the HBP was not available. If patients had performed more than one MR imaging study, we considered just the first available MR imaging study unless the patient had performed another MRI study, and the difference of the Model For End-Stage Liver Disease (MELD) score at the time of the two studies was higher than 3. In nine patients, we included two gadoxetic acid–enhanced MRI examinations.

MR imaging

Both gadobenate dimeglumine–enhanced MRI and gadoxetic acid–enhanced MRI examinations were performed on 1.5 T MR systems (Table 1) with a phased-array body coil. Patients of the gadobenate dimeglumine group received a dose of 0.1 mmol/kg body weight of gadobenate dimeglumine at a rate of 2 ml/s through a cubital intravenous line, followed by a 30 ml of 0.9% saline at the same speed. Patients of the gadoxetic acid group received a dose of 0.025 mmol/kg body weight of gadoxetic acid at a rate of 1 ml/s, through a cubital intravenous line followed by a 20 ml of 0.9% saline flush at the same speed.

The contrast-enhanced sequences consisted of axial 3-dimensional breath-hold, T1-weighted, gradient echo sequences, known as gradient-recalled-echo. The contrast-enhanced MRI protocols as well as the parameters of the gradient-recalled-echo sequence used before and after contrast agent injection are shown in Table 1. The hepatobiliary phase was acquired using a fixed delay at 90 min or at 20 min after the injection of gadobenate dimeglumine or gadoxetic acid, respectively. The liver MRI protocol also included axial in-

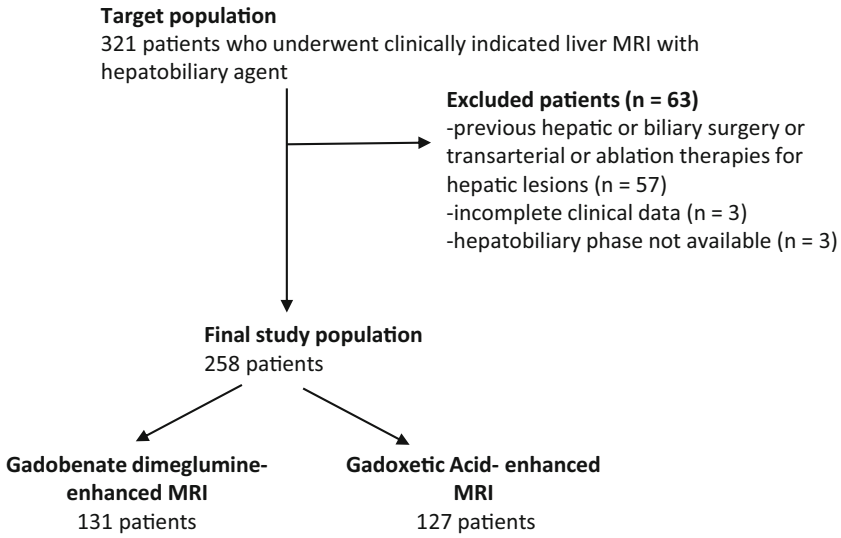

Fig. 1 Flowchart of study enrolment based on recommended Strengthening the Reporting of Observational Studies in Epidemiology guidelines [14]. MRI, magnetic resonance imaging

and opposed-phase T1-weighted images, single-shot T2-weighted, and respiratory-triggered fat-suppressed turbo spin-echo T2-weighted and diffusion-weighted images.

Clinical data and MELD score

We reviewed the medical records to assess demographic information and laboratory results for each patient.

Of note, the diagnosis of cirrhosis was confirmed at pathology in 81 of 249 patients (32.5%), including 60 patients at center 1 and 21 patients at center 2. In the remaining 168 patients, the diagnosis of cirrhosis had been made by combining clinical and laboratory data with liver elastography (i.e., acoustic radiation force impulse elastography and/or transient elastography) [15, 16].

Firstly, we collected the following patient-related factors which could potentially impact the adequacy of the HBP: sex, age, etiology of liver cirrhosis, and indication for liver MRI. Serum total bilirubin, creatinine, and INR measured within 3 months before or after liver MRI examination were also retrieved, and the MELD score was calculated using the following formula MELD score = 10 × ((0.957 × ln(creatinine)) + (0.378 × ln(bilirubin)) + (1.12 × ln(INR))) + 6.43 [10]. The demographic as well as the clinical data of the study population in the two centers is summarized in Table 2.

Adequacy of the hepatobiliary phase: imaging analysis

By using the institutions' picture archiving and communication systems (PACS - Impax, Agfa in both centers), the images of the MRI studies were reviewed. Two readers with 30- (A.V.) and 5 years (C.K.C.) of experience reviewed the MRI examinations of gadobenate dimeglumine group. Two readers with 17- (G.B.) and 4-year (F.V.) experience reviewed the MRI examination of gadoxetic acid group. The readers were blinded to the MELD score. The performance of gadobenate dimeglumine–enhanced MRI and gadoxetic acid–enhanced MRI in obtaining an adequate HBP in cirrhotic patients was analyzed with both a quantitative and qualitative assessment.

Quantitative assessment

The readers placed in consensus round-shaped region of interest (ROIs) of 0.5 cm^2 size to measure the signal intensities of the liver parenchyma and of the psoas muscle both in the unenhanced phase and in the HBP. A total of five ROIs were drawn: two in the right lobe (anterior and posterior segments), two in the left lobe (lateral and medial segments), and one in the right psoas muscle (Fig. 2). Focal hepatic lesions, major branches of portal or hepatic veins, areas of confluent fibrosis, and artifacts were avoided. ROIs were copied from the pre-contrast to the HBP images to ensure identical size and location. The signal intensity ratio (SIR) between the average value of the four signal intensities of the liver parenchyma, and the value of SI of the psoas muscle was calculated both for the unenhanced phase (SIR pre) and for the HBP (SIR post). The contrast enhancement index (CEI) was calculated as follow: CEI = SIR post/SIR pre [17].

We tested the influence of MELD score on the degree of CEI along with the difference between the mean CEI in the gadobenate dimeglumine and gadoxetic acid groups adjusted for the MELD score.

Qualitative assessment

The readers reviewed in consensus the HBPs to make a visual assessment of the signal intensity of the liver relative to the intrahepatic vessels as validated by Tamada et al [18]. The

Table 1 MR liver protocol and parameters of the gradient echo sequence in the two centers

	Gadobenate dimeglumine–enhanced MRI ($n = 131$) University of Milan	Gadoxetic acid–enhanced MRI ($n = 127$) University of Palermo	
Post-contrast dynamic phases			
Arterial (s[a])	25–35	25–35	
Portal venous (s[a])	60–80	60–80	
equilibrium (s[a])	120–150	None	
transitional (min[a])	None	3, 5, and 10	
hepatobiliary (min[a])	90	20	
MR scanner	1.5 T system (Achieva, Philips Healthcare)	1.5 T system (Signa Excite HD, GE Healthcare)	1.5 T system (Achieva, Philips Healthcare)
Gradient echo sequence			
Repetition time (ms)	3.92	3.8	4.6
Echo time (ms)	1.82	1.8	2.2
Flip angle	9	12	10
Slice thickness (mm)	4	4.4	4
Overlap (mm)	2	2	–
Number of partitions	60	50	83
Bandwidth (Hz/pixel)	434	83.33	381
Field of view (mm)	385 × 305	300 × 240	375 × 351
Matrix	192 × 305	352 × 224	188 × 319
Acquisition time (s)	21	19	21

[a] Time after contrast agent injection

MRI magnetic resonance imaging

HBP was defined as adequate when the signal intensity of the hepatic vessels was lower compared to the liver parenchyma. The HBP was defined inadequate when the signal intensity of the vessels was equal or higher compared to the liver parenchyma. Representative examples illustrating these criteria on both gadobenate dimeglumine–enhanced MRI and gadoxetic

Table 2 Demographic characteristics, clinical features, and MELD score of the study population

	Gadobenate dimeglumine–enhanced MRI ($n = 131$)	Gadoxetic acid–enhanced MRI ($n = 118$)	p value
Sex n (%)			0.358
Men	92 (70.2)	89 (75.4)	
Women	39 (29.8)	29 (24.6)	
Age (years), mean (SD) [min–max]	61.2 (11.2) [30–87]	67.8 (10.8) [32–84]	< 0.0001
Etiology of liver cirrhosis n (%)			
Type C viral hepatitis	61 (46.6)	79 (66.9)	
Type B viral hepatitis	17 (13.0)	13 (11.0)	
Alcohol abuse	20 (15.3)	2 (1.7)	
Nonalcoholic fatty liver cirrhosis	9 (6.9)	12 (10.2)	
Primary biliary cirrhosis	4 (3.0)	1 (0.8)	
Cryptogenic cirrhosis	6 (4.6)	5 (4.2)	
Hemochromatosis	1 (0.7)	1 (0.8)	
Mixed type C and type B hepatitis	0 (0)	2 (1.7)	
Mixed type B hepatitis and alcohol abuse	2 (1.5)	1(0.8)	
Mixed type C hepatitis and alcohol abuse	8 (6.1)	1 (0.8)	
Mixed nonalcoholic fatty liver cirrhosis and alcohol abuse	3 (2.3)	1 (0.8)	
MELD score			
Mean (SD) [min–max]	11.42 (4.05) [6.4–24.6]	9.87 (3.81) [6.4–25.6]	0.0022
Subgroups of MELD score n (%)			0.0118
MELD < 10 (%)	59 (45)	75 (63.6)	
MELD 10–15 (%)	50 (38.2)	32 (27.1)	
MELD > 15 (%)	22 (16.8)	11 (9.3)	

MELD model for end-stage liver disease, *MRI* magnetic resonance imaging, *SD* standard deviation

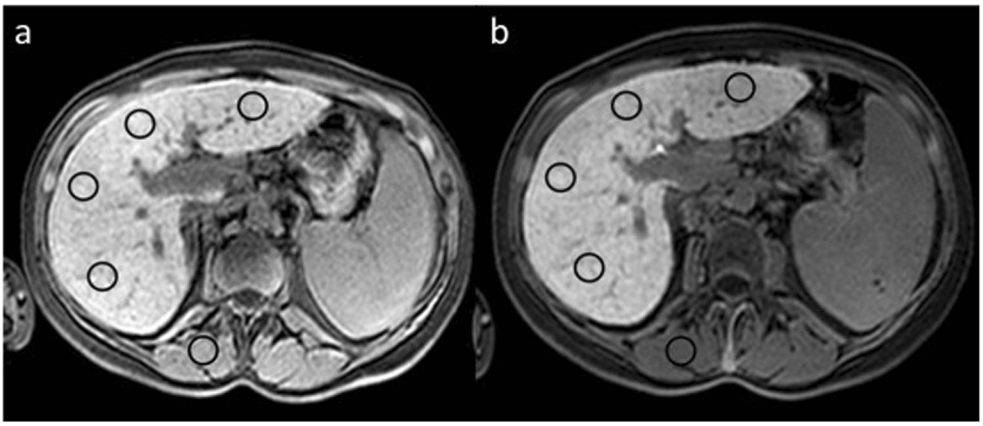

Fig. 2 Demonstration of placement of the region of interest in a 68-year-old man with known cirrhosis submitted to gadobenate dimeglumine–enhanced MRI. **a** Three-dimensional breath-hold, T1-weighted, gradient-recalled echo axial MR image obtained before injection of gadobenate dimeglumine–enhanced MRI shows the placement of the four regions of interest in the liver parenchyma, two in the medial and lateral segments of the left lobe, and two in the anterior and posterior segments of the right lobe, and of one region of interest in the paravertebral muscles for the measurement of signal intensities. **b** Three-dimensional breath-hold, T1-weighted, gradient-recalled echo axial MR image in the hepatobiliary phase obtained after injection of gadobenate dimeglumine–enhanced MRI shows the placement of the four regions of interest in the liver parenchyma, two in the medial and lateral segments of the left lobe, and two in the anterior and posterior segments of the right lobe, and of one region of interest in the paravertebral muscles for the measurement of signal intensities

acid–enhanced MRI MR studies are shown in Figs. 3 and 4, respectively. We analyzed the difference between the two contrast agents on qualitative assessment adjusted for MELD score.

Statistical analysis

Descriptive statistics were produced for the demographic and clinical characteristics. Continuous variables were expressed with regard to their distribution as mean (SD), minimum and maximum. Discrete variables were expressed as absolute numbers and percentages. Student's *t* test was used to test differences in continuous variables and the chi-squared test to test differences regarding categorical data.

The primary endpoint of our study was to compare the performance of gadobenate dimeglumine–enhanced MRI and gadoxetic acid–enhanced MRI in obtaining an adequate HBP in cirrhotic patients with different MELD score. For this comparison, the following analyses were performed:

1. Regression analysis between CEI ratio between the two contrast agent and MELD score (i.e., gadobenate dimeglumine and gadoxetic acid groups). More precisely, we estimated the regression between CEI and MELD score within each group using a simple linear

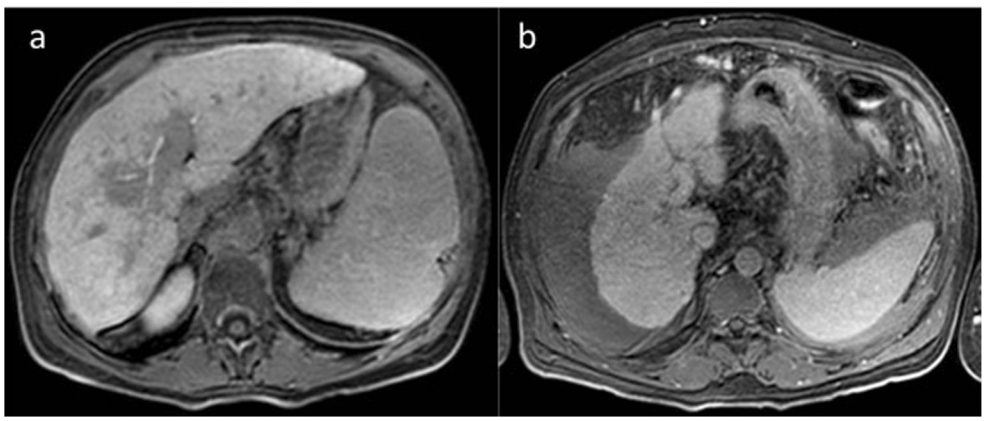

Fig. 3 Demonstration of the adequacy/inadequacy of the hepatobiliary phase in gadobenate dimeglumine–enhanced MRI. **a** Three-dimensional breath-hold, T1-weighted, gradient-recalled echo axial MR image in the hepatobiliary phase obtained after injection of gadobenate dimeglumine–enhanced MRI in a 50-year-old man with MELD score 9 shows an adequate hepatobiliary phase as demonstrated by the hyperintensity of the liver parenchyma compared to portal vein. **b** Three-dimensional breath-hold, T1-weighted, gradient-recalled echo axial MR image in the hepatobiliary phase obtained after injection of gadobenate dimeglumine–enhanced MRI in a 58-year-old woman with MELD score 17 shows an inadequate hepatobiliary phase as demonstrated by the isointensity of the liver parenchyma compared to portal vein

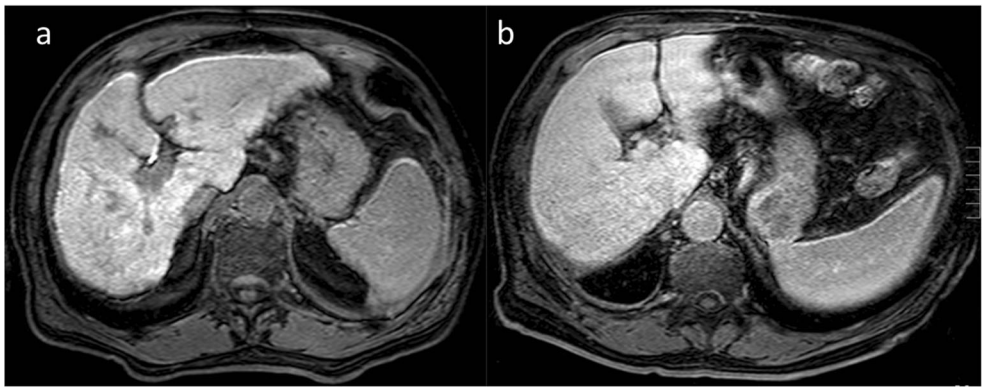

Fig. 4 Demonstration of the adequacy/inadequacy of the hepatobiliary phase in gadoxetic acid–enhanced MRI. **a** Three-dimensional breath-hold, T1-weighted, gradient-recalled echo axial MR image in the hepatobiliary phase obtained after injection of gadoxetic acid–enhanced MRI in a 76-year-old man with MELD score 8 shows an adequate hepatobiliary phase as demonstrated by the hyperintensity of the liver parenchyma compared to portal vein. **b** Three-dimensional breath-hold, T1-weighted, gradient-recalled echo axial MR image in the hepatobiliary phase obtained after injection of gadoxetic acid–enhanced MRI in a 83-year-old man with MELD score 18 shows an inadequate hepatobiliary phase as demonstrated by the isointensity of the liver parenchyma compared to portal vein

regression-correlation analysis. Then, a multiple linear regression analysis was used to study the difference between the CEI of the two groups adjusted by MELD score.

2. A two-way analysis of the covariance (MELD score and contrast agent) to compare the difference of the mean CEI between the two contrast agents among the three groups of MELD score—MELD < 10, MELD between 10 and 15, and MELD > 15—and within each group of MELD score.
3. Analysis of dichotomous variable—adequate vs. inadequate HBP—among the three groups of MELD score and within each group of MELD score (specific odds ratio by MELD score group). This analysis was followed by a multiple logistic regression analysis to investigate the difference on qualitative evaluation between the two contrast agents adjusted by the statistically significant MELD score.

Analyses were performed by using SPSS v.24.0 (IBM Corp.). The $p < 0.05$ was considered significant.

Results

Study population

Our study population consisted of 249 cirrhotic patients (mean age 64.8 years ± 11.4; range 30–87 years), including 181 men (64.2 years, ± 11.0; 32–86 years), and 68 women (66.6 years, ± 12.4; age range, 30–87 years). A total of 258 liver MRI studies, 131 performed with gadobenate dimeglumine, and 127 with gadoxetic acid were included in the study.

The gadobenate dimeglumine and gadoxetic acid groups did not differ significantly for demographics and clinical features except for age with patients imaged with gadoxetic acid being older than patients imaged with gadobenate dimeglumine (Table 2). The MELD score was significantly different among the gadobenate dimeglumine and gadoxetic acid groups ($\chi^2 = 8.874$, $p = 0.118$) with a higher percentage of patients of the gadobenate dimeglumine group having a MELD score > 15 (16.8% and 9.3%, respectively).

Adequacy of the hepatobiliary phase

The analysis of the quantitative assessment showed that the CEI was significantly higher in the gadoxetic acid group compared to the gadobenate dimeglumine group in the overall study population ($p = 0.002$, Table 3). The mean CEI in the three subgroups of MELD score (i.e., MELD < 10, MELD between 10 and 15, and MELD > 15) was significantly different ($p < 0.000001$). Of note, the not significant difference within the third group (i.e., MELD > 15) may be related to the low number of patients in this subgroup. A poor CEI was predicted by elevated values of MELD score for both gadoxetic acid and gadobenate dimeglumine groups, with a pooled regression coefficient of − 0.013. Therefore, an increase of one unit of the MELD score was found to lower the CEI of 0.013 (ES 0.005; $p = 0.014$; CI 95%, 0.02–0.003; in percentage, 1.3% with CI 95% 2–0.3%). At equal values of MELD score, the CEI in the gadoxetic acid group was increased by 0.23 (ES, 0.043; $p < 0.0001$; CI 95%, 0.14–0.31; in percentage, 23% with CI 95%, 14%–31%) in comparison to the gadobenate dimeglumine group (Fig. 5). Of note, this difference between the two agents is adjusted by the statistically significant difference in MELD score between the two groups.

The analysis of the qualitative assessment showed that the adequacy of the HBP was significantly higher for gadoxetic acid group compared to the gadobenate dimeglumine group ($\chi^2 = 26.72$, $p = 0.000$) (Table 3). The odds ratio (OR) to have

Table 3 Assessment of the adequacy of hepatobiliary phase in the gadobenate dimeglumine and gadoxetic acid groups, stratified in different categories by the MELD score

	Gadobenate dimeglumine–enhanced MRI ($n = 131$)	Gadoxetic acid–enhanced MRI ($n = 127$)	Odds ratio (ES, z)	p value
Quantitative assessment				
Contrast enhancement index, mean (SD)				
Overall	1.36 (0.265)	1.60 (0.410)		0.002
Contrast enhancement index, mean (SD)				< 0.000001
MELD < 10	1.39 (0.245)	1.64 (0.40)		< 0.0001
MELD 10–15	1.35 (0.27)	1.57 (0.44)		0.005
MELD > 15	1.27 (0.29)	1.49 (0.41)		0.089
Qualitative assessment				
Adequate n (%)				
Overall	60 (45.8)	98 (77.2)	3.64	< 0.001
MELD < 10	35	57	1.95 (0.37, 1.81)	0.073
MELD 10–15	23	34	7.98 (0.56, 3.73)	0.002
MELD > 15	2	7	17.5 (0.97, 2.95)	0.0318
Inadequate n (%)	71 (54.2)	29 (22.8)		
MELD < 10	24	19		
MELD 10–15	27	6		
MELD > 15	20	4		

MELD model for end-stage liver disease, *MRI* magnetic resonance imaging, *SD* standard deviation, *ES* standard error

an adequate HBP was 3.64 in the gadoxetic acid group compared to that in gadobenate dimeglumine. Of note, this result is adjusted to take into account the statistically significant difference in MELD score between gadoxetic acid group and the gadobenate dimeglumine group. In addition, this difference in adequacy of the HBP between the gadoxetic acid group and the gadobenate dimeglumine group was maintained when stratifying patients into three categories by MELD score (Table 3). Moreover, the adequacy of HBP in the gadoxetic acid group compared to the gadobenate dimeglumine group increased with the increase of the MELD score (OR (interaction) = 1.233; $p = 0.011$; CI 95%, 1.05–1.45).

Discussion

In this study, we speculated that in cirrhotic patients, the different percentage of hepatocytes uptake of gadobenate dimeglumine and gadoxetic acid might result into higher hepatic parenchymal enhancement in the HBP with gadoxetic acid in patients with damaged hepatic parenchyma. The results of our quantitative evaluation confirmed this hypothesis: the mean CEI was higher in the gadoxetic acid group compared to the gadobenate dimeglumine group. Filippone et al [19] showed similar results to ours. In their study, gadoxetic acid–enhanced MRI demonstrated significantly superior enhancement of the hepatic parenchyma in the HBP in both cirrhotic and non-cirrhotic patients when compared with gadobenate dimeglumine–enhanced MRI. Their study, however, was limited by the relatively small number of cirrhotic patients ($n = 64$), the lack of available Child-Pugh class in 18 patients and deviations from the currently recommended protocol [1] concerning the contrast dose, and the acquisition time of HBP.

To our knowledge, this is the first study demonstrating that in cirrhotic patients; the adequacy of the hepatobiliary phase with gadoxetic acid–enhanced MRI is better compared to gadobenate dimeglumine–enhanced MRI. In particular, our results showed an inverse correlation between the CEI and the MELD score in cirrhotic patients. Specifically, an increase of one unit of the MELD score lowered the CEI by 1.3%. Interestingly, the impact of the increase of the MELD score on the reduction of hepatic parenchymal enhancement in the HBP was the same in both groups. These results are clinically important because they show that the degree of hepatic uptake of the hepatobiliary contrast agents is dependent on the functional status of the liver [20–23], and that an impaired hepatic function leads to a suboptimal HBP [11, 19, 24]. A suboptimal HBP would potentially result in lower capability of detection and characterization of focal liver lesions in cirrhotic patients with high MELD score.

We noticed with interest that in patients with the same MELD score, the CEI was 23% higher in the gadoxetic acid

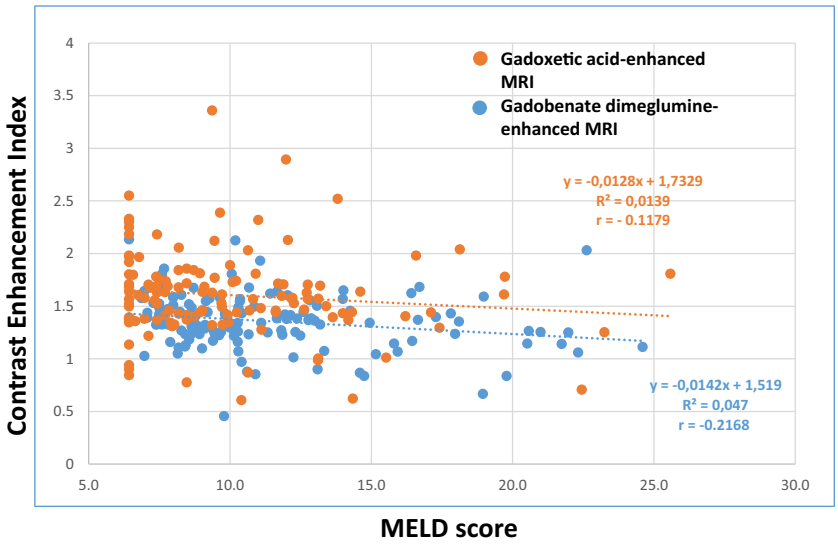

Fig. 5 Scatter plot of the correlation between the Contrast Enhancement Index and Model for End-Stage Liver Disease score in the gadoxetic acid and gadobenate dimeglumine groups. MELD, Model For End-Stage Liver Disease, MRI, Magnetic resonance imaging

group compared to that in gadobenate dimeglumine. Therefore, at certain levels of MELD score, an adequate HBP might be achieved with gadoxetic acid–enhanced MRI and not with gadobenate dimeglumine–enhanced MRI. These results are not surprising and can be explained with the higher hepatocyte uptake of gadoxetic acid (50%) in comparison to gadobenate dimeglumine (3–5%). According to our results, gadoxetic acid–enhanced MRI should be preferred to gadobenate dimeglumine–enhanced MRI in cirrhotic patients with MELD score > 10 if the HBP phase is clinically indicated. However, further research is needed to identify whether there is a MELD number above which an adequate hepatobiliary phase cannot be achieved.

The performance of gadoxetic acid and gadobenate dimeglumine in obtaining an adequate HBP in cirrhotic patients with different levels of MELD score was also assessed and compared with a *qualitative* analysis. Of note, we preferred the evaluation of MELD score rather than Child-Pugh score because the latter contains clinical data (encephalopathy and ascites) which can be observer dependent, and they were not retrospectively available in all patients at the time of index MR. MELD score is observer independent and gives a continuous numeric scale. An adequate HBP is important in cirrhotic patients because the hypointensity in the hepatobiliary phase is considered an ancillary feature for the categorization of observations according to the Liver Imaging Reporting and Data System (LIRADS) v. 2018 [25]. In our study, the adequacy of the HBP was visually assessed through liver-to-portal vein contrast ratio, a simple and reliable method that can be used as an alternative to quantitative analysis [18]. In agreement with the results of our quantitative analysis, the overall percentage of adequate HBP was higher in gadoxetic acid group than in gadobenate dimeglumine group. This result can be once again explained by the higher hepatocyte uptake of gadoxetic acid in comparison to gadobenate dimeglumine. In patients with normal liver function (MELD <10), the adequacy of HBP was slightly better for gadoxetic acid-enhanced MRI, but this result was not statistically significant ($p = 0.07$). In patients with advanced cirrhosis (MELD > 15), the efficacy of gadoxetic acid–enhanced MRI in providing an adequate HBP was 17 fold higher compared to gadobenate dimeglumine–enhanced MRI. Based on our results, we infer that in patients with high MELD score, the administration of the hepatobiliary agent could be useless; anyhow, if it is clinically indicated, we recommend to use gadoxetic acid given the higher probability of obtaining clinically relevant information.

Our study had limitations. First, it was a retrospective study, and the cirrhotic patients were not consecutively sent to MRI examinations. Second, the imaging studies and the imaging analysis were carried out in two centers with different scanners and by different readers. Due to the use of different sequence parameters for acquisition of both contrast agents, we cannot be sure if the data are truly comparable. Anyhow, the use of visual parameters of enhancement (liver/vessel signal intensity) and the use of signal intensity ratios should decrease the error caused by different scanners and sequence parameters. Third, we had a faculty physician and a resident read in consensus in each center, without any measures of inter- or intraobserver variability, which limits the generalizability of our study results. However, the parameters evaluated were either quantitative or required the simple evaluation of liver enhancement in comparison to vessel enhancement. Fourth, the biochemical values used to calculate the MELD score were tested in different laboratories, which might constitute a source of bias. Fifth, there was a significant difference between the subgroups of MELD score between the two centers: there were more patients with severe liver dysfunction in

the group included in the University of Milan, probably because this is a liver transplant center; nevertheless, the multiple linear regression analysis was adjusted for MELD score to overcome this difference. Sixth, we did not obtain a pathologic correlation with histologic severity of cirrhosis, and subsequently, it was not possible to assess the prognostic meaning of our results that need to be confirmed with a prospective study.

In conclusion, the results of our study show that HBP is negatively affected by the severity of cirrhosis for both the hepatobiliary contrast agents but suggest the use of gadoxetic acid–enhanced MRI to have an adequate HBP in cirrhotic patients, especially in patients with high MELD score.

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Methodology
- retrospective
- cross-sectional study
- multicenter study

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