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Can functional parameters from hepatobiliary phase of gadoxetate MRI predict clinical outcomes in patients with cirrhosis?

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Abstract

Objectives To determine the value of quantitative parameters of gadoxetate-enhanced magnetic resonance imaging (MRI) in predicting prognosis in patients with cirrhosis.

Methods A cohort of 63 cirrhotic patients who had gadoxetate MRI and 2-year clinical follow-up was enrolled. Enhancement ratio (ER), contrast enhancement index (CEI) and contrast enhancement spleen index (CES) were calculated. The usefulness of these parameters and clinical scores, such as Child-Pugh score (CPS) and model for end stage liver disease (MELD), in predicting adverse outcomes, such as variceal bleeding (VB), hepatic encephalopathy (HE) and mortality at 2 years were evaluated.

Results Fifteen, 31 and 27 patients, respectively, had VB, HE and mortality within 2 years. The ER at 15 min (ER 15) and CES at 20 min (CES 20) were found to be the best MRI predictors. Areas under the receiver operating characteristic curve (AUC) for predicting VB were 0.785, 0.729, 0.673, 0.714, respectively, for ER 15, CES 20, CPS and MELD scores. ER 15 of less than 48 had sensitivity of 96% and specificity of 84% for predicting onset of HE within 2 years.

Conclusions In patients with cirrhosis, ER 15 or CES 20 were equivalent or better predictors of major morbidity and mortality compared with commonly used clinical scores.

Key Points
• *Gadoxetate parameters may identify cirrhotic patients at risk of adverse events.*
• *Gadoxetate parameters usually show superior predictive values compared to clinical scores.*
• *CES 20 score is associated with risk of mortality within 2 years.*

Keywords Liver cirrhosis · Patient outcome assessment · Magnetic resonance imaging · Gadolinium · Hepatic encephalopathy

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Introduction

Assessment of liver function and prognosis in patients with cirrhosis is of substantial clinical interest to hepatologists. When seeing patients with cirrhosis in the clinic, it is often difficult for the hepatologist to predict which patients require close follow-up, changes in medical therapy or other empirical intervention. Current methods of hepatic function assessment include the indocyanin green clearance test, galactose elimination capacity test and clinical scoring systems such as the model for end-stage liver disease (MELD) score and Child-Pugh score.

Indocyanin green (ICG) clearance has been used to determine the operative risk before hepatectomy, as well as to evaluate donor liver function in transplantation [1, 2]. However,

this study is rarely performed in Europe or the USA. Child-Pugh score was developed mainly to assess the operative risk in cirrhotic patients undergoing transjugular portosystemic shunt. Problems in the use of this system include subjective assessment of hepatic encephalopathy and difficulty in determining small amounts of ascites clinically. MELD score was originally developed to predict mortality in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS), and then used to prioritise organ allocation in patients awaiting liver transplantation [3, 4]. It can more accurately predict death within a 3-month period than Child-Pugh score [5].

MRI with hepatocyte-specific contrast agent gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA; gadoxetate disodium, henceforth called gadoxetate) is not only advantageous in the detection and characterisation of liver morphological information, such as the presence of hepatocellular cancer, but also may have a potential role in assessment of liver function [6, 7]. About 50% of gadoxetate is taken up in hepatocytes by multi-specific organic anion transporter proteins and then excreted into biliary canaliculi via the multidrug resistant proteins [8]. Gadoxetate uptake and elimination pathways are related to hepatocyte function and there is suboptimal uptake in patients with impaired liver function [9]. Several studies have reported the role of MRI with gadoxetate in the assessment of liver function [7, 10–17]. These studies reported significant correlation of gadoxetate enhancement with routinely used liver function tests, Child-Pugh score and MELD score. However, we are not aware of any study assessing the prognostic value of gadoxetate-enhanced magnetic resonance imaging (MRI), in particular, for predicting adverse clinical outcomes, such as the onset of hepatic encephalopathy or gastrointestinal variceal bleeding. We wanted to assess the value of quantitative parameters from gadoxetate-enhanced MRI in independently predicting adverse outcomes in patients with cirrhosis.

Materials and methods

Patients

For this retrospective Health Insurance Portability and Accountability Act (HIPAA)-compliant study, the radiology database was searched for MRI examinations with gadoxetate between January 2011 and December 2013. Institutional review board permission was obtained for retrospective assessment of imaging and clinical data with waiver of informed consent. Initial search revealed 235 patients who were scanned for assessment of cirrhosis. Figure 1 shows the inclusion and exclusion criteria and the derivation of the cohort. After the exclusion criteria, an adequate cohort remained for analysis of outcomes.

Sixty-three patients (mean age, 59.2 years; 33 men/30 women) were enrolled in the study. Laboratory data including international normalised ratio (INR), serum sodium, serum creatinine, serum albumin, serum ammonia, total bilirubin, platelet count and clinical outcomes, including onset (if any) of encephalopathy or variceal bleeding, liver transplantation and mortality within 2 years of MRI were collected from the electronic medical records.

MRI technique

MRI examinations were performed using a 1.5-T MRI scanner (Magnetom Avanto or Symphony; Siemens, Erlangen, Germany). MRI parameters are given in Table 1. Post-contrast phases were obtained in arterial, portal venous, 3-min, 5-min, 10-min, 15-min and 20-min delayed phases after infection of 0.025 mmol/kg body weight of gadoxetate sodium (Primovist or Eovist; Bayer HealthCare, Leverkusen, Germany).
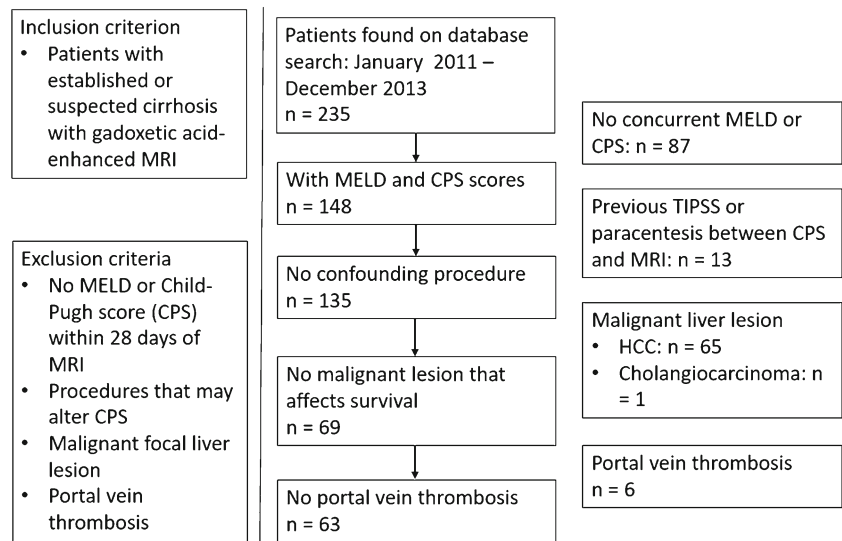
Image evaluation

The image evaluation was performed by a single reader blinded to the laboratory data and clinical follow-up. Regions of interest (ROIs) measuring 2 cm^2 were placed in the liver, the right paraspinal muscle and spleen (avoiding areas of artefact, vessels and masses) on pre- and post-contrast (15 and 20 min) images. In 15 of the 63 patients, a second reviewer independently drew ROIs to assess interobserver correlation of the parameters from gadoxetate MRI. The following ratios were calculated: enhancement ratio of liver at 15 and 20 min (ER 15 and ER 20) from the equation: [liver signal intensity (SI) at 15 (20) min – liver SI pre-contrast]/(liver SI pre-contrast); contrast enhancement index at 15 and 20 min (CEI 15, CEI 20) according to the formula: [liver SI at 15 (20) min / muscle SI at 15 (20) min]/(liver SI pre-contrast / muscle SI pre-contrast); contrast enhancement spleen index at 15 and 20 min (CES 15, CES 20) according to the equation: [liver SI at 15 (20) min / spleen SI at 15(20) min]/(liver SI pre-contrast / spleen SI pre-contrast).

Statistical analysis

Univariate analysis was performed with analysis of variance (ANOVA) with Bonferroni correction. ANOVA determined differences in gadoxetate-derived quantitative parameters and clinical scores between patients with and without adverse outcomes, such as variceal bleeding. Stepwise logistic regression analysis was performed to find the best independent predictor(s) of the clinical outcomes. At each step, the likelihood ratio test was used to determine if the parameter was to be entered in the model. Receiver operating characteristic (ROC) curve analysis was used to evaluate the optimal

Fig. 1 Inclusion and exclusion criteria and derivation of cohort

Inclusion criterion
- Patients with established or suspected cirrhosis with gadoxetic acid-enhanced MRI

Exclusion criteria
- No MELD or Child-Pugh score (CPS) within 28 days of MRI
- Procedures that may alter CPS
- Malignant focal liver lesion
- Portal vein thrombosis

Patients found on database search: January 2011 – December 2013
n = 235

With MELD and CPS scores
n = 148

No confounding procedure
n = 135

No malignant lesion that affects survival
n = 69

No portal vein thrombosis
n = 63

No concurrent MELD or CPS: n = 87

Previous TIPSS or paracentesis between CPS and MRI: n = 13

Malignant liver lesion
- HCC: n = 65
- Cholangiocarcinoma: n = 1

Portal vein thrombosis
n = 6

sensitivity and specificity of the selected signal intensity ratios in predicting clinical outcomes of cirrhosis [18, 19]. A p value of less than 0.05 was used to indicate statistical significance. Statistical analysis was performed using MedCalc 11.1 (for ROC curves; MedCalc Software, Mariakerke, Belgium) and PASW 18.0. (SPSS, Chicago, IL, USA).

Results

Patients

All patients were followed in the hepatology clinic for known or suspected cirrhosis. The diagnosis of cirrhosis was made on all patients with liver biopsy ($n = 24$), transient elastography ($n = 55$), imaging features of cirrhosis on computed tomography (CT) or MRI ($n = 43$) using previously reported criteria [20–22], or magnetic resonance elastography ($n = 7$). Several patients had more than one confirmatory test. The patients' demographics, aetiology of liver disease, laboratory values and clinical outcomes are shown in Table 2. The most common aetiology for liver disease were hepatitis C and non-

alcoholic steatohepatitis (NASH), accounting together for 59% (37/63) of cases. Fifteen patients died within 1 year of MRI and 27 patients within 2 years.

Interobserver correlation

A subset of 15 patients were assessed by two reviewers. The intraclass correlation coefficient between the gadoxetate parameters of the two reviewers for ER 15, ER 20, CEI 15, CEI 20, CES 15 and CES 20 were 0.989, 0.988, 0.938, 0.728, 0.977 and 0.967, respectively, indicating a very strong positive correlation between the two readers' measurements.

Correlation between MRI parameters and clinical scores

The gadoxetate-MRI-derived parameters for each group of Child-Pugh and MELD classes are shown in Table 3. There was a significant difference between Child groups A, B and C for all the parameters. Similarly, there were significant differences in means of all parameters for MELD groups of ≤10, 11-20 and >20.

Table 1 Sequence details

	TR (ms)	TE (ms)	Flip angle	ST (mm)	RBW
T1-weighted gradient echo	123	2.2 or 4.93[a]	70	7.0	445
T2-weighted HASTE	1,110	95	150	5.0	475
T1-weighted fat-suppressed three-dimensional gradient echo [b]	4.98	2.27	12	3.0	300
Diffusion-weighted imaging	1,500	71	90	6.0	1,735

TR repetition time, *TE* echo time, *ST* slice thickness, *NEX* number of excitations, *RBW* receiver bandwidth in Hz/pixel, *HASTE* half-Fourier acquisition single-shot turbo spin echo

[a] Echo time of 2.2 ms for out-of-phase, 4.93 ms for in-phase

[b] Performed before and after intravenous gadoxetate

Table 2 Patient epidemiology, laboratory and outcome data

Characteristic	Number of patients (%) (n = 63)
Age (mean, range - in years)	59.2 (25-79)
Male	33 (53%)
Female	30 (47%)
Aetiology of liver disease [a]	
Hepatitis C	21 (33%)
NASH[b]	16 (25%)
Alcohol	13 (21%)
Hepatitis B	5 (8%)
Biliary [c]	5 (8%)
Other	9 (14%)
Child-Pugh class	
A	24 (38%)
B	22 (35%)
C	17 (27%)
MELD score	
≤10	32 (51%)
11-20	26 (41%)
>20	5 (8%)
Laboratory values	
Serum creatinine (mean ± SD) in mg/dL	0.94 ± 0.43
Serum bilirubin (mean ± SD) in mg/dL	2.82 ± 4.28
Serum albumin (mean ± SD) in g/dL	3.22 ± 0.76
INR (mean ± SD)	1.36 ± 0.34
Clinical outcomes at 2 years [a]	
Hepatic encephalopathy	31 (49%)
Variceal bleeding	15 (24%)
Orthotropic liver transplant	14 (22%)
Mortality	27 (43%)

[a] Some patients had more than one aetiology for liver disease or more than one outcome in 2 years' follow-up

[b] Non-alcoholic steatohepatitis

[c] Primary or secondary sclerosing cholangitis

Clinical outcomes

Table 4 gives the results of univariate ANOVA for the gadoxetate parameters and clinical scores. There was a significant difference in means for ER 15 and CES 20 between those with and without variceal bleeding ($p = 0.047$ and 0.033, respectively) (Figs. 2 and 3) and those with and without encephalopathy ($p < 0.001$ for both ER 15 and CES 20) (Figs. 2 and 4). Patients with adverse outcome had lower values of these parameters.

Figure 5 shows the receiver operating characteristic (ROC) curves for ER 15 and CES 20 (which showed the best univariate analysis results among MRI parameters) as well as MELD and Child-Pugh scores. Figure 5a shows the ROC curves for prediction of death within 2 years. MELD score had the highest area under curve (AUC) of 0.825 [95% confidence interval (CI), 0.690-0.918]. This was higher, but not significantly so, than the AUC of Child-Pugh score (0.736; 95% CI, 0.590-0.851; $p = 0.130$), ER 15 (0.741; 95% CI, 0.595-0.855; $p = 0.196$) and CES 20 (0.764; 95% CI, 0.621-0.874; $p = 0.367$). A CES 20 score below 1.0 had a sensitivity of 68.9% (95% CI, 41.3-89.0) and specificity of 69.7% (95% CI, 51.3-84.4) for predicting mortality within 2 years.

Figure 5b shows the curves for variceal bleeding within 2 years of MRI. ER 15 had the highest AUC of 0.785 (95% CI, 0.646-0.889). This was significantly higher than the AUC of Child-Pugh score (AUC = 0.673; 95% CI, 0.526-0.799; $p = 0.030$) but not significantly higher than that of MELD score (AUC 0.714; 95% CI, 0.569- 0.833; $p = 0.336$) or CES 20 (AUC = 0.729; 95% CI, 0.585-0.845; $p = 0.501$). ER 15 of less than 37.6 had sensitivity of 68.7% (95% CI, 34. -90.1) and specificity of 73.7% (95% CI, 56.9-86.6) for predicting variceal bleeding within 2 years.

Figure 5c shows the ROC curves for the prediction of hepatic encephalopathy within 2 years. ER 15 had the highest AUC of 0.931 (95% CI, 0.823-0.983). However, this was not significantly higher compared to the AUC of Child-Pugh score (0.914; 95% CI, 0.800-0.975; $p = 0.570$), MELD score (0.843; 95% CI, 0.713- 0.931; $p = 0.131$) and CES 20 (0.890; 95% CI, 0.769-0.961; $p = 0.218$). ER 15 of less than 48.0 had a sensitivity of 96.0% (95% CI, 79.6-99.9) and specificity of 84.0% (95% CI, 63.9-95.5) for predicting onset of hepatic encephalopathy within 2 years.

Since there was a strong correlation between imaging parameters and clinical scores, multivariate logistic regression analysis was performed to determine the independent effect of imaging parameters on predicting outcome. On multivariate logistic regression, both ER 15 and CES 20 significantly predicted the onset of variceal bleeding within 2 years of MRI ($p = 0.04$ and 0.03, respectively). MELD and Child-Pugh scores were not significant on this analysis ($p = 0.37$ and 0.82, respectively). Encephalopathy within 2 years was best predicted by Child-Pugh score ($p = 0.003$) and CES 20 ($p = 0.033$). The other imaging parameters and MELD score ($p = 0.52$) were not significant. The MELD score and CES 20 significantly predicted death within 2 years of MRI ($p = 0.02$, both). No parameter was able to predict death within 1 year or the need for orthotropic liver transplant within 2 years.

Discussion

It is known that gadoxetate-induced enhancement is dependent on hepatic perfusion, vascular permeability, extracellular transport and hepatocyte uptake [23]. Patients with cirrhosis have impairment of all these physiological processes.

Table 3 Gadoxetate signal intensity ratios in each Child-Pugh and MELD class

	ER 15	ER 20	CEI 15	CEI 20	CES 15	CES 20
All (n = 63)	56.2 (42.7)	62.1 (48.5)	1.4 (0.3)	1.4 (0.4)	1.1 (0.3)	1.1 (0.3)
Child A (n = 23)	79.2 (25.9)	82.4 (29.6)	1.6 (0.2)	1.7 (0.3)	1.3 (0.3)	1.4 (0.3)
Child B (n = 22)	38.7 (35.1)	54.0 (52.3)	1.2 (0.3)	1.3 (0.4)	0.9 (0.2)	1.0 (0.2)
Child C (n =17)	45.6 (56.2)	42.9 (56.1)	1.3 (0.2)	1.2 (0.2)	1.0 (0.1)	1.0 (0.1)
p values	0.002	0.024	<0.001	<0.001	<0.001	<0.001
MELD (≤ 10) (n = 32)	67.6 (31.7)	74.8 (35.9)	1.5 (0.3)	1.6 (0.4)	1.2 (0.3)	1.3 (0.3)
MELD (11-20) (n = 26)	48.6 (52.9)	56.2 (58.8)	1.3 (0.3)	1.3 (0.4)	1.0 (0.2)	1.0 (0.1)
MELD (> 20) (n = 5)	21.9 (10.7)	11.1 (7.6)	1.3 (0.2)	1.2 (0.2)	1.0 (0.2)	1.0 (0.2)
p values	0.039	0.015	0.011	0.006	0.019	<0.001

Figures given are the mean (standard deviation) for each group

For Child and MELD classes *p* values for each gadoxetate parameter are given using ANOVA

ER 15, ER 20 enhancement ratio at delayed 15 or 20 min, respectively

CEI 15, CEI 20 contrast enhancement index at delayed 15 or 20 min, respectively

CES 15, CES 20 contrast enhancement spleen index at delayed 15 or 20 min, respectively

Presence of extracellular collagen reduces diffusivity of gadoxetate and also the proportion of functioning hepatocytes per voxel [24]. Bilirubin uses the same organic anion transport system as gadoxetate and is a competitive agonist [25]. Hence, elevation in direct bilirubin is likely to cause reduced uptake of gadoxetate [26]. In addition, the expression of the organic anion transport systems has been shown to reduce in rats with advanced liver fibrosis [27]. Therefore, it is reasonable to hypothesise that gadoxetate enhancement indices are markers of hepatocyte function, and may have a role in predicting complications of cirrhosis.

Several studies have demonstrated a strong association between gadoxetate enhancement indices and pathologically determined liver fibrosis stage [6, 23, 24, 28, 29]. Other studies addressed the value of preoperative MRI with gadoxetate in prediction of liver failure after major liver surgery [30–32]. A

Table 4 ANOVA of clinical scores and imaging parameters by outcome

		CPS	MELD	ER 15	ER 20	CEI 15	CEI 20	CES 15	CES 20
Died within 1 year	No (n = 49)	7.33 (2.18)	10.01 (6.99)	53.20 (35.27)	63.06 (46.62)	1.39 (0.34)	1.44 (0.41)	1.06 (0.23)	1.11 (0.25)
	Yes (n = 14)	8.04 (2.61)	12.25 (8.61)	60.98 (53.19)	60.40 (52.27)	1.38 (0.30)	1.43 (0.36)	1.14 (0.31)	1.21 (0.34)
	p[a]	0.255	0.263	0.488	0.834	0.902	0.930	0.264	0.205
Died within 2 years	No (n = 36)	7.26 (2.09)	9.92 (7.35)	54.40 (36.74)	63.22 (47.80)	1.40 (0.35)	1.45 (0.42)	1.07 (0.24)	1.12 (0.27)
	Yes (n = 27)	8.04 (2.63)	12.05 (8.00)	58.38 (49.85)	60.59 (50.10)	1.35 (0.29)	1.41 (0.34)	1.12 (0.29)	1.19 (0.32)
	p[a]	0.199	0.275	0.717	0.832	0.549	0.652	0.434	0.311
Variceal bleeding	No (n = 48)	7.33 (2.42)	9.78 (7.18)	61.49 (41.87)	64.34 (44.11)	1.40 (0.31)	1.45 (0.37)	1.13 (0.28)	1.19 (0.31)
	Yes (n = 15)	8.47 (2.00)	14.35 (8.36)	39.14 (42.38)	54.72 (61.56)	1.30 (0.37)	1.40 (0.46)	0.97 (0.13)	1.01 (0.15)
	p[a]	0.107	0.043	0.047	0.506	0.281	0.683	0.036	0.033
Encephalopathy	No (n = 32)	6.19 (1.58)	6.90 (4.36)	74.29 (44.77)	80.06 (47.00)	1.50 (0.31)	1.58 (0.38)	1.19 (0.29)	1.30 (0.32)
	Yes (n = 31)	9.02 (2.17)	14.97 (8.21)	37.45 (31.48)	43.46 (43.19)	1.26 (0.30)	1.28 (0.35)	0.98 (0.17)	0.99 (0.14)
	p[a]	<0.001	<0.001	<0.001	0.002	0.003	0.002	0.001	<0.001
Orthotopic liver transplant	No (n = 49)	7.42 (2.36)	11.08 (8.44)	58.89 (46.80)	63.15 (51.29)	1.40 (0.35)	1.46 (0.42)	1.10 (0.27)	1.17 (0.29)
	Yes (n = 14)	8.43 (2.24)	10.88 (4.05)	44.78 (23.73)	55.53 (38.54)	1.30 (0.22)	1.32 (0.26)	1.06 (0.24)	1.04 (0.25)
	p[a]	0.162	0.947	0.283	0.610	0.313	0.233	0.581	0.152

Figures given are the mean (standard deviation) for each group

ER 15, ER 20 enhancement ratio at delayed 15 min or 20 min, respectively

CEI 15, CEI 20 contrast enhancement index at delayed 15 min or 20 min, respectively

CES 15, CES 20 contrast enhancement spleen index at delayed 15 min or 20 min, respectively

Variceal bleeding, Encephalopathy and *Transplant* relate to occurrences within 2 years of MRI

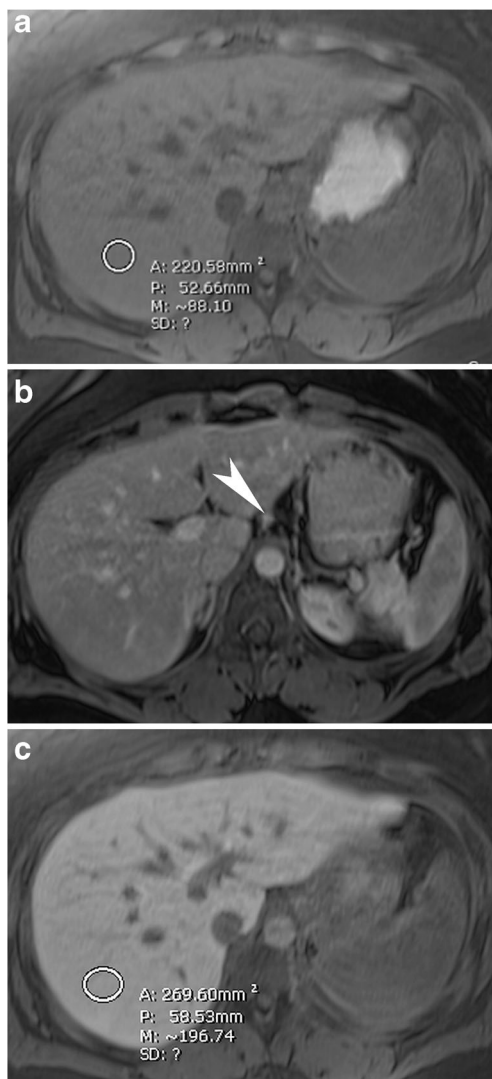[a] Significance values on ANOVA with Bonferroni correction

Fig. 2 A 34-year-old woman with hepatitis C virus-induced cirrhosis. Axial T1-weighted images pre-contrast (**a**), post-gadoxetate venous (**b**) and 15-min (**c**) phases are shown. The enhancement ratio at 15 min (ER 15) was 124. Contrast-enhancement index at 20 min (CEI 20) was 2.2. These are high indices suggesting good hepatocyte function. MELD score was 5.3 and Child Pugh score was 4. The patient had small varices (*arrow*, **b**) but no variceal bleeding or encephalopathy during a 3.5-year follow-up period

Fig. 3 A 69-year-old man with hepatitis C virus-induced cirrhosis. Axial T1-weighted images pre-contrast (**a**), post-gadoxetate venous (**b**) and 15-min (**c**) phases are shown. Image **b** shows hepatic hydrothorax (*arrow*) and small paraesophageal varies (*arrowheads*). The ER 15 was 58 and the CEI 20 was 1.4, suggesting modest hepatocyte function. MELD score was 18.2 and Child Pugh score was 10. The patient had an episode of variceal bleeding 7 months after the MRI and was transplanted 18 months later. He had no episode of encephalopathy

study of 73 patients [31] found that after major liver resection, patients with liver failure had significantly lower relative enhancement at 20 min than those without liver failure ($p =$ 0.009). Two studies with 150 and 328 patients [16, 33] demonstrated that enhancement ratio at 20 min correlated with MELD score ($p <0.001$ for both). In addition, studies have assessed the transit time for gadoxetate to be excreted in bile ducts to be associated with liver disease and Child-Pugh score [14, 34]. Our findings are consistent with this strong association between gadoxetate-related enhancement parameters and MELD and Child-Pugh groups. However, we are not aware of any publications investigating the value of gadoxetate-enhanced MRI in the prediction of prognosis in patients with
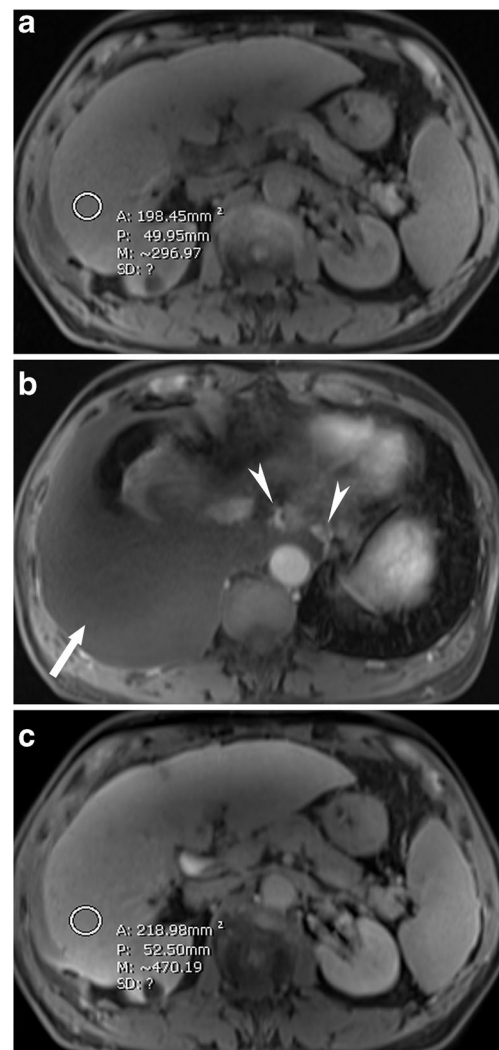
liver disease. In this study, we investigated the prediction of major adverse outcomes of liver disease, including variceal bleeding, hepatic encephalopathy, and death using gadoxetate-related enhancement indices.

Gastrointestinal bleeding in patients with cirrhosis may be due to variceal or non-variceal bleeding. About 30% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis have varices at the time of diagnosis [35]. The annual rate of a first haemorrhage episode among those with varices is about 12% and each episode of active variceal haemorrhage is associated with 15-20% mortality [36, 37]. Varices are found when portal venous pressure exceeds 10 mmHg [38]. Prediction of variceal bleeding is of
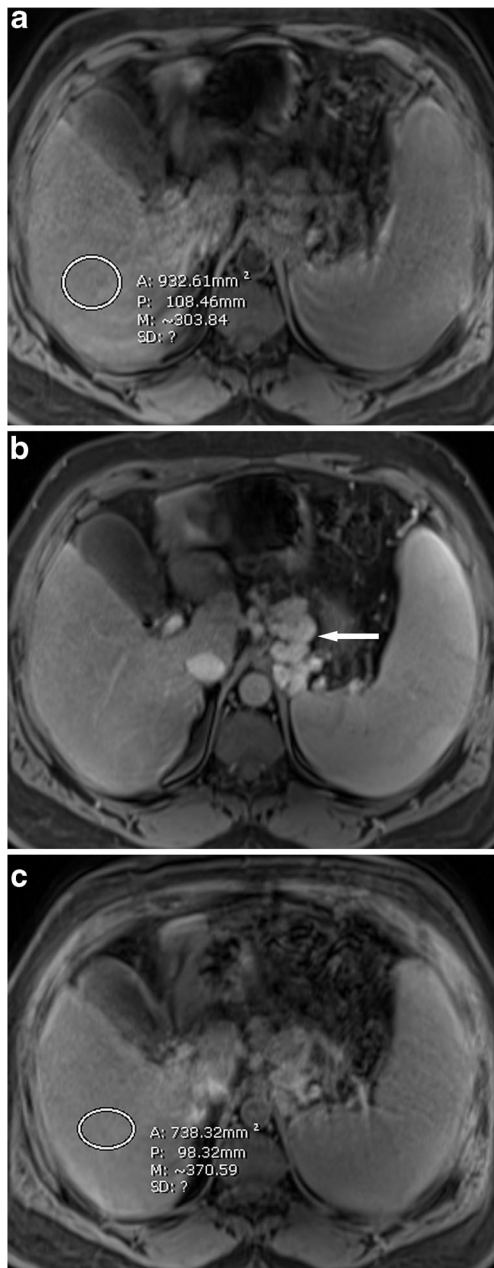
Fig. 4 A 50-year-old man with hepatitis C virus-induced cirrhosis. Axial T1-weighted images pre-contrast (**a**), post-gadoxetate venous (**b**) and 15-min (**c**) phases are shown. Image **b** shows large perisplenic varices (*arrow*) and splenomegaly. The ER 15 was 22 and the CEI 20 was 1.0, suggesting poor hepatocyte function. MELD score was 16.2 and Child Pugh score was 9. The patient had three episodes of hepatic encephalopathy in the two years after the MRI. He had no episode of gastrointestinal bleeding

substantial interest to hepatologists [39–42]. Knowing that a patient is at high risk of variceal bleeding allows a change in management which includes administering non-selective beta-blockers, such as nadolol, and endoscopic band ligation [43]. Our results suggest that ER 15 and CES 20 were better predictors of variceal bleeding than MELD and Child-Pugh scores. ER 15 of less than 37.6 had sensitivity of 69% and
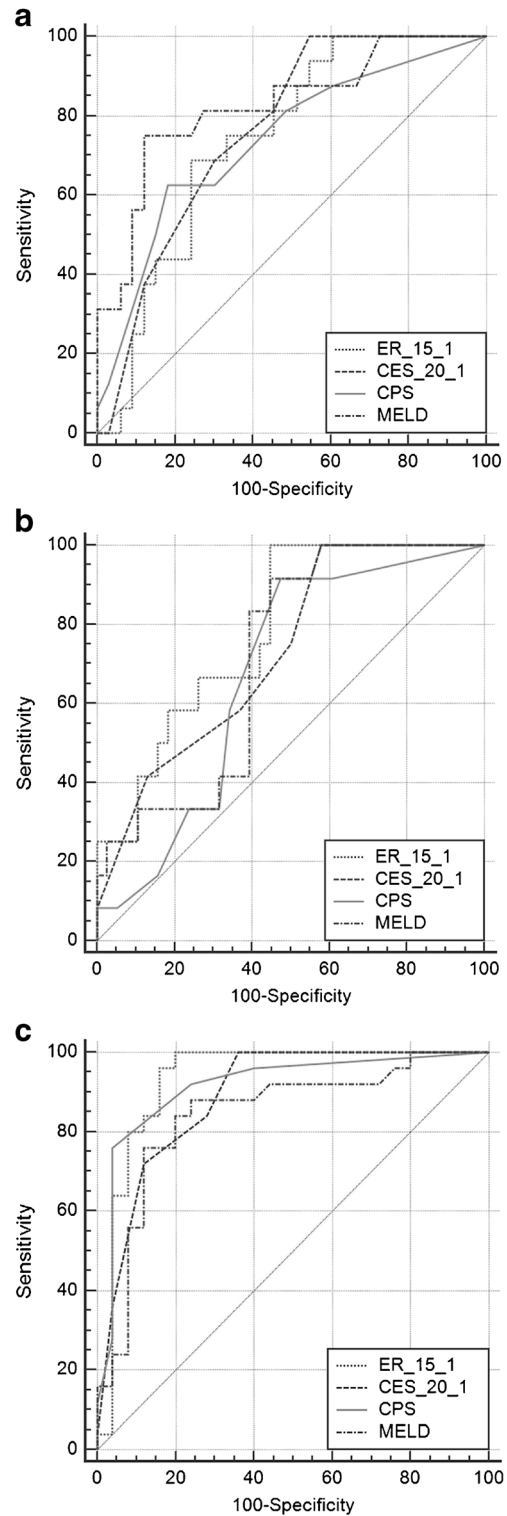

Fig. 5 Receiver operating characteristics (ROC) curves plotting sensitivity (*y*-axis) and 1 - specificity (*x*-axis) of enhancement ratio at 15 min (*ER 15*), contrast enhancement spleen index at 20 min (*CES 20*), Child-Pugh score (*CPS*) and *MELD* score in determining mortality (**a**), variceal bleeding (**b**) and hepatic encephalopathy (**c**) within 2 years. *Diagonal line* represents an area under curve (AUC) of 0.50. AUC values of MRI parameters and clinical scores are given in the text

specificity of 74% for predicting variceal bleeding within 2 years.

Hepatic encephalopathy, including early cases diagnosed with psychometric testing, is seen in about 50% of patients with cirrhosis [44, 45]. There is a wide spectrum of diseases from mild neuropsychiatric symptoms, such as insomnia, to coma. Imaging studies, such as T1-mapping, 1-hydrogen and 32-phosphorus MR spectroscopy may show brain abnormalities in patients with hepatic encephalopathy [46–48], but are not clinically used. Symptomatic patients are usually treated with non-absorbable disaccharides, such as lactulose, and non-absorbable antibiotics, such as rifaximin [49, 50]. Our study showed that ER 15 and CES 20 were abnormally low in patients at risk of hepatic encephalopathy. For instance, an ER 15 of less than 48.0 had sensitivity of 96% and specificity of 84% for predicting onset of hepatic encephalopathy within 2 years. We believe that reduced enhancement with gadoxetate is a predictor of suboptimal hepatocyte function and impaired ammonia clearance. Accurate predictions of hepatic encephalopathy may lead to initiation of prophylactic therapy [51–53].

Neither MELD score nor imaging parameters were able to predict death within 1 year. However, CES 20 and MELD score predicted increased risk of mortality within 2 years on multivariate logistic regression ($p = 0.02$ for both). CES 20 score below 1.0 had a sensitivity of 69% and specificity of 70% for predicting mortality within 2 years. In addition, neither clinical scores nor signal intensity parameters were able to predict the need for liver transplant within 2 years in our study. This may be attributed to the complicated process of listing for transplant including the need for good cardiac function and absence of alcohol or drugs in serum and urine. In addition, timing of liver transplant is related to availability of a suitable donor.

Our study shows that patients with high MELD scores and low CES 20 and ER 15 are at risk of multiple adverse outcomes, including variceal bleeding, hepatic encephalopathy and death within 2 years. We are aware of limitations of our study. Foremost is the retrospective nature of the study. Our cohort number ($n = 63$) was small and our findings will need to be validated by larger studies. The patients in this study were scanned on 1.5-T MRI. We did not scan patients on 3.0-T MRI. Nevertheless, it has been reported that gadoxetate enhancement indices are not dependent on the magnetic field strength in either a normal population or in patients with cirrhosis [54]. We only investigated parameters of gadoxetate-enhanced MRI and did not include other MRI findings, such as liver or spleen stiffness on MR elastography or the presence of varices. In addition, the large standard deviation in ANOVA analysis may reduce the usefulness of conclusions from this test. Further studies are needed to investigate whether MRI may be a one-stop examination to give functional and prognostic information about patients with cirrhosis.

In conclusion, this retrospective study of selected cohort with cirrhosis shows that signal intensity parameters after gadoxetate were valuable in identifying patients at risk of adverse events such as variceal bleeding, independently of clinical scores, such as the MELD score. The two best MRI predictors were enhancement ratio at 15 min (ER 15) and contrast enhancement spleen index at 20 min (CES 20).

Compliance with ethical standards

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