Digestive and Liver Disease 51 (2019) 1438–1445

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Estimating liver function in a large cirrhotic cohort: Signal intensity of gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI☆

Davide Ippolito[c,1], Simone Famularo[a,b,*,1], Alessandro Giani[a,b], Eleonora Benedetta Orsini[a,c], Anna Pecorelli[a,c], Enrico Pinotti[a,b], Davide Gandola[a], Fabrizio Romano[a,b], Sandro Sironi[a,e], Davide Paolo Bernasconi[d], Luca Gianotti[a,b]

[a] School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy
[b] Department of Surgery, San Gerardo Hospital, Monza, Italy
[c] Department of Radiology, San Gerardo Hospital, Monza, Italy
[d] Center of Biostatistic for Clinical Epidemiology, University of Milan-Bicocca, Monza, Italy
[e] Department of Diagnostic Radiology, Papa Giovanni XXIII Hospital, Bergamo, Italy

ARTICLE INFO

Article history:
Received 21 August 2018
Accepted 5 April 2019
Available online 30 May 2019

Keywords:
Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI
Liver function test
Liver cirrhosis
Magnetic resonance imaging

ABSTRACT

Background: To assess whether gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI study is useful to estimate liver function in comparison to the presence or absence of cirrhosis, Child Pugh (CP), Model for End-stage Liver Disease (MELD), ALBI scores and biochemical test.
Methods: We retrospectively reviewed all consecutive Gd-EOB-DTPA-enhanced-MRI studies performed between 2010 and 2016 in patients with focal liver lesions undergoing clinical evaluation. Patients were divided in study and control group according to the presence of cirrhosis, and then classified by CP, MELD and ALBI. Signal intensity was calculated through the liver-to-muscle ratio in portal- (SI-POR) and hepatobiliary-phase(SI-HEP).
Results: Three-hundred-three Gd-EOB-DTPA liver-enhanced-MRI studies were included. One-hundred-ninety-one patients (63%) were cirrhotic. SI-HEP was significantly lower in cirrhotic group (0.55 ± 0.29 vs 0.66 ± 0.40, $p = 0.004$).The SI-HEP progressively decreased from CP-A to CP-C (0.59 ± 0.28 to 0.25 ± 0.19, $p < 0.0001$) and a significant difference was found between MELD ≤ 9 and MELD > 9 groups (0.61 ± 0.31 vs 0.49 ± 0.28, $p = 0.007$). No differences between ALBI grades were evident. Among biochemical parameters a moderate correlation was found among SI-HEP and total bilirubin, AST and albumin.
Conclusion: SI-HEP after Gd-EOB-DTPA-enhanced-MRI effectively stratified patients with different Child Pugh grades and MELD scores. This technique could hence be useful as a novel radiological marker to estimate the underlying liver function.

1. Introduction

The assessment of liver function is currently made through non-invasive methods. Clinical scoring systems are routinely used in daily clinical practice to estimate the severity of liver disease [1]. The two more performing scoring systems are the Child-Pugh score and the Model for End-Stage Liver Disease (MELD), however recently the ALBI score has been introduced in clinical practice as a less subjective score than the Child score. MRI nowadays plays a central role in the clinical work-up of patients with liver disorders and it is currently used in an increasing number of cirrhotic patients as well as in other focal lesion diseases, even more in patients scheduled for liver surgery. Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA Primovist®, Bayer Healthcare, Berlin), is a paramagnetic hepatobiliary magnetic resonance (MR) contrast agent for T1-weighted imaging, excreted into the biliary system without being metabolized [2]. Recent stud-

☆ Part of these results were presented at EASL' International Liver Congress 2018 (Paris, 11–15 April 2018), and another part has been presented at the 13th IHPBA World Congress 2018 (Geneva, Switzerland, 04–07 September 2018) (https://www.ihpba2018.com/).

* Corresponding author at: Department of Surgery (4° piano A), San Gerardo Hospital, Via Pergolesi 33, 20900 Monza, Italy.
E-mail address: simone.famularo@gmail.com (S. Famularo).

[1] Ippolito D. and Famularo S. have contributed the same at this manuscript.

https://doi.org/10.1016/j.dld.2019.04.009
1590-8658/

ies have explored the relationship between the enhancement and liver function [2,3], and different methods were employed to estimate its intensity. However, the correlation between liver function scores (as Child-Pugh score, MELD score, ALBI score), or biochemical parameters and signal intensity (SI) were investigated in few and small cirrhotic cohorts. In this perspective, we retrospectively analyzed a large consecutive cohort of healthy and cirrhotic livers which were evaluated at the surgical outpatient clinic for a first assessment of a liver focal lesion. The aim was to evaluate whether the hepatobiliary phase SI, obtained by Gd-EOB-DTPA-enhanced MRI, was related to liver function tests and scores as Child-Pugh, MELD and ALBI. The signal intensity has been obtained by a new approach based on liver-to-muscle ratio.

2. Materials and methods

2.1. Study overview and variables

The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013). Local Ethical Committees review of the protocol deemed that formal approval was not required owing to the retrospective, observational and anonymous nature of this study. Results are reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [4].

We retrospectively reviewed all consecutive patients undergoing their first evaluation for liver focal lesion at our surgical outpatient clinic in the period between May 2010 and September 2016. Patients may have been referred to our attention by other physicians rather than general practitioners, for further specialistic evaluation. Consequently not every patient had been submitted to surgery, according to best clinical practice, and all of them had been followed-up.

Patients were eligible in the study if they met the following inclusion criteria: (1) a Gd-EOB-DTPA-enhanced-MRI performed at our institution to investigate a focal liver lesion; (2) a regular follow-up at our hospital; (3) laboratory data available at least for 30 days around the date of each MRI included in the study. Exclusion criteria were: previous transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), or the execution of a MRI without available blood samples and clinical evaluation.

After enrollment, patients were divided in a control and a study group according to the absence or the presence of liver cirrhosis. Diagnosis of liver cirrhosis was made before our outpatient evaluation, and it was based on laboratory values and clinical findings or radiological findings. After enrollment, cirrhosis was confirmed by an expert hepatologist of the same institution. The Child-Pugh score was obtained as previously described [5] as well as the MELD score [6] and the ALBI score [7].

2.2. Data handling

Data collection was performed using an electronic database system collected prospectively. Clinical and laboratory data were retrospectively recorded in blind by three surgeons on the date (±30 days) of each MRI execution. Three radiologist performed the evaluation of MRI images, in blind respect to the previous diagnosis and clinical and laboratory results. Then, data were centrally combined. The submitted data were then checked by the other authors and, once examined, the records were accepted into the dataset for the analysis.

2.3. Outcomes

The primary aim of our study was to evaluate whether the hepatobiliary phase SI, obtained at Gd-EOB-DTPA-enhanced MRI studies, was related to cirrhosis, Child-Pugh, MELD and ALBI scores, in a large cohort of consecutive patients with healthy and cirrhotic livers. The second aim was to appraise the correlation between hepatobiliary phase (SI-HEP) and biochemical liver function tests. SI-HEP has been evaluated with a new approach employing the liver-to-muscle ratio.

2.4. Image technique

All patients underwent an upper abdominal examination on a 1.5T magnet (Achieva Plus, Philips, The Netherlands), using a 16-channel phased-array body coil. The standard liver imaging protocol included: axial T1-weighted in and out of phase breath-hold spoiled gradient-echo (GE) sequences, axial and coronal turbo spin-echo T2-weighted, respiratory-triggered, and fat-suppressed sequences, and axial 3D T1-weighted fat-suppressed spoiled recalled-echo sequences (THRIVE). The dynamic images were obtained before and after intravenous injection of 0.1 mL/kg of gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA, Primovist, Bayer, Leverkusen, Germany), with a flow rate of 1 mL/sec and followed by a 30-mL saline flush at the same rate, using a power injector and acquiring four different phases (arterial, portal, transitional and hepatobiliary) [8]. A real-time display, by using fluoroscopic technique, returned low-resolution images every second in order to allow breath-held coordination with contrast up to the level of celiac trunk, in order to acquire the arterial phase of hepatic enhancement. The portal (or interstitial) and the transitional phase were acquired respectively 70 s and 140 s after the arterial phase. The hepatobiliary phase was acquired 20 min after the arterial phase.

2.5. Image analysis

The mean signal intensity values of the liver and paravertebral muscle were measured on precontrast, portal and hepatobiliary phase Gd-EOB-DTPA-enhanced T1-weighted images by using operator-defined region-of-interest (ROI) methods. For every sequence, each radiologist outlined three ROIs in the liver (2 in the right lobe, 1 in the left lobe), excluding liver lesions, visible blood vessels, or imaging artifacts and one ROI in the paravertebral muscles. Each ROI was drawn centrally, far from peripheral zone, in order to obtain the higher signal intensity, as reported by previous published study [9]. To obtain comparable measurements before and after Gd-EOB-DTPA administration, ROIs were placed in exactly corresponding positions on every image.

To quantify the enhancement during portal (POR) and hepatobiliary (HEP) phase, the relative liver-to-muscle ratio which compares the mean value of signal intensity of ROI drawn in liver and muscle, was calculated in both different phases:

irPOR = (icPORl/icPORm) – (icPREl/icPREm)/(icPREl/icPREm)

irHB = (icHBl/icHBm) – (icPREl/icPREm)/(icPREl/icPREm)

*(ir = intensity ratio; ic = intensity contrast; PRE = precontrast; l = liver; m = muscle).

2.6. Statistical analysis

Before the analysis, far outliers (i.e values laying under the first quartile or over the third quartile of more than 3 times the interquartile range) of some continuous variables (enhancements and biochemical parameters) were excluded.

Descriptive analysis was performed using mean, standard deviation and quartiles for continuous variables and absolute numbers and percentages for categorical variables. The empirical distribution of the enhancements was described using histograms, revealing approximately a gaussian shape. The interobserver agree-

ment of the measurements was evaluated by computing the intraclass correlation coefficient.

Child-Pugh score was categorized as usual in grade A (score: 5–6), grade B (7–9) and C (10–15). MELD score was categorized in 2 subgroups dividing healthy liver from hepatopathy [10]: score ≤9 and score >9. The ALBI score grading was also considered: grade 1 (score ≤ −2.60), grade 2 (−2.60 < score ≤ −1.39) and grade 3 (score > −1.39).

The association between the enhancements and the categorical variables of the liver function (presence/absence of cirrhosis, Child-Pugh grade, categorized MELD score and ALBI grade) was analyzed using box-plots and the T-test for the comparison of means or one-way ANOVA and the Tukey HSD test.

The association between the enhancements and the biochemical parameters was quantified using the Spearman correlation index.

Finally, a Receiver Operating Characteristics (ROC) curve analysis was employed to assess the discrimination performance of the hepatobiliar enhancement with respect to presence/absence of cirrhosis and the categories of Child-Pugh grade (A vs B or C). The optimal cut-off value was established based on the Youden index and the corresponding sensitivity, specificity, positive predictive value and negative predictive value are provided. The Area Under the ROC Curve (AUC) index was also computed with the 95% confidence interval.

All the analyses were performed using R software version 3.4. Statistical tests are two tailed and p-values below 5% are considered significant.

3. Results

A total of 303 consecutive Gd-EOB-DTPA-enhanced MRI studies, performed in 221 consecutive patients, were included in the study. The intraclass correlation coefficient was 0.82 for the hepatobiliary and 0.72 for the portal enhancement, suggesting an overall good interobserver agreement. The majority of studies were taken from males (186 [61.4%]) and mean age at MRI examination was 67.7 ± 12.9 years (range 28–87). Forty-five patients performed more than one MRI study and, for each imaging, new blood tests and clinical assessments were performed. However, as a sensitivity analysis, we assessed the association between liver functional scores and the enhancements considering only the first visit for each patient (221 records). As shown in the Supplementary Table 1 and Fig. 1, the results confirm the conclusions of the analysis on all 303 records.

3.1. Liver function and radiological characteristics in cirrhotic and non-cirrhotic patients

One hundred ninety-one [63.0%] Gd-EOB-DTPA-enhanced MRI studies were performed on cirrhotic patients, of whom 116 [38.3%] detectable at radiology.

Among cirrhotic patients the Child-Pugh score was available for 186 (97.4%) observations and the median Child-Pugh score was 5 (IQR 5–6); 153/186 (82.3%) studies belonged to Child-Pugh class A, 24/186 (12.9%) to Child-Pugh class B and 9/186 (4.8%) to Child-Pugh class C. Among cirrhotic patients the MELD score was available for 180 (94.2%) observations and the median MELD score value was 8.76 (IQR 6.79–11.13); 92/180 (51.1%) patients had a MELD score ≤9 and 88/180 (48.9%) >9. Among cirrhotic patients the ALBI score was available for 182 (95.3%) observations and the median ALBI score was −2.49 (IQR −2.93; −2.22); 75/182 (41.2%) studies belonged to ALBI grade 1, 101/182 (55.5%) to ALBI grade 2 and 6/182 (3.3%) to ALBI grade 3 (Table 1). Considering the whole population, signal intensity after 20 min injection of Gd-EOB-DTPA (hepatobiliary phase) had a mean value of 0.59 (±0.34), significantly higher than SI in portal phase (0.34 ± 0.21), p < 0.0001. The increase of signal intensity from portal to hepatobiliary phase remained significant also when patients were divided between cirrhotic (from 0.35 ± 0.21 to 0.55 ± 0.29, p < 0.0001) and non-cirrhotic (from 0.33 ± 0.20 to 0.66 ± 0.40, p < 0.0001). Axial planes of 3D fat sat T1-weighted images before and after injection of Gd-EOB-DTPA with operator-defined region-of-interest (ROI), differentiated for presence of cirrhosis versus not, are depicted in Fig. 1.

Table 1
Patients' demographics, liver function and radiological characteristics. SI-HEP hepatobiliary phase signal intensity; SI-POR portal phase signal intensity; MELD model for end stage liver disease; ALBI albumine-bilirubine.

Factors	Univariate statistics N = 303
Sex, male (%)	186 (61.4)
Age, years	
Mean (sd)	63.77 (12.89)
Median [IQR]	65.35 [55.00, 74.39]
SI-HEP	
Mean (sd)	0.59 (0.34)
Median [IQR]	0.57 [0.38, 0.78]
SI-POR	
Mean (sd)	0.34 (0.21)
Median [IQR]	0.33 [0.20, 0.46]
Cirrhosis, yes (%)	191 (63.0)
CHILD score among cirrhotics	
Mean (sd)	5.82 (1.40)
Median [IQR]	5.00 [5.00, 6.00]
Missing (%)	5 (2.6)
CHILD grade among cirrhotics	
A (%)	153 (82.35)
B (%)	24 (12.9)
C (%)	9 (4.8)
Missing (%)	5 (2.6)
MELD score among cirrhotic patients	
Mean (sd)	9.21 (3.58)
Median [IQR]	8.74 [6.76, 11.00]
Missing (%)	11 (5.8)
MELD category among cirrhotic patients	
≤9 (%)	92 (51.1)
>9 (%)	88 (48.9)
Missing (%)	11 (5.8)
ALBI score among cirrhotics	
Mean (sd)	−2.54 (0.59)
Median [IQR]	−2.49 [−2.93, −2.22]
Missing (%)	9 (4.7)
ALBI grade among cirrhotics	
1 (%)	75 (41.21)
2 (%)	101 (55.49)
3 (%)	6 (3.3)
Missing (%)	9 (4.7)

3.2. Association between liver function and enhancements

The mean (standard deviation) values of SI in portal and hepatobiliary phase in cirrhotic and non-cirrhotic groups and among Child-Pugh classes (A–C), MELD classes (≤9, >9) and ALBI grade (1–3) are summarized in Table 2. The same stratification was applied to describe the empirical distribution of the enhancements using boxplots (Fig. 2 for SI-HEP and Supplementary Fig. 2 for SI-POR).

Hepatobiliary enhancement in cirrhotic livers was significantly lower than in non-cirrhotic livers (0.55 ± 0.29 vs 0.66 ± 0.40, p = 0.004) while no difference regarding portal enhancement was observed (0.35 ± 0.21 vs 0.33 ± 0.20, p = 0.491).

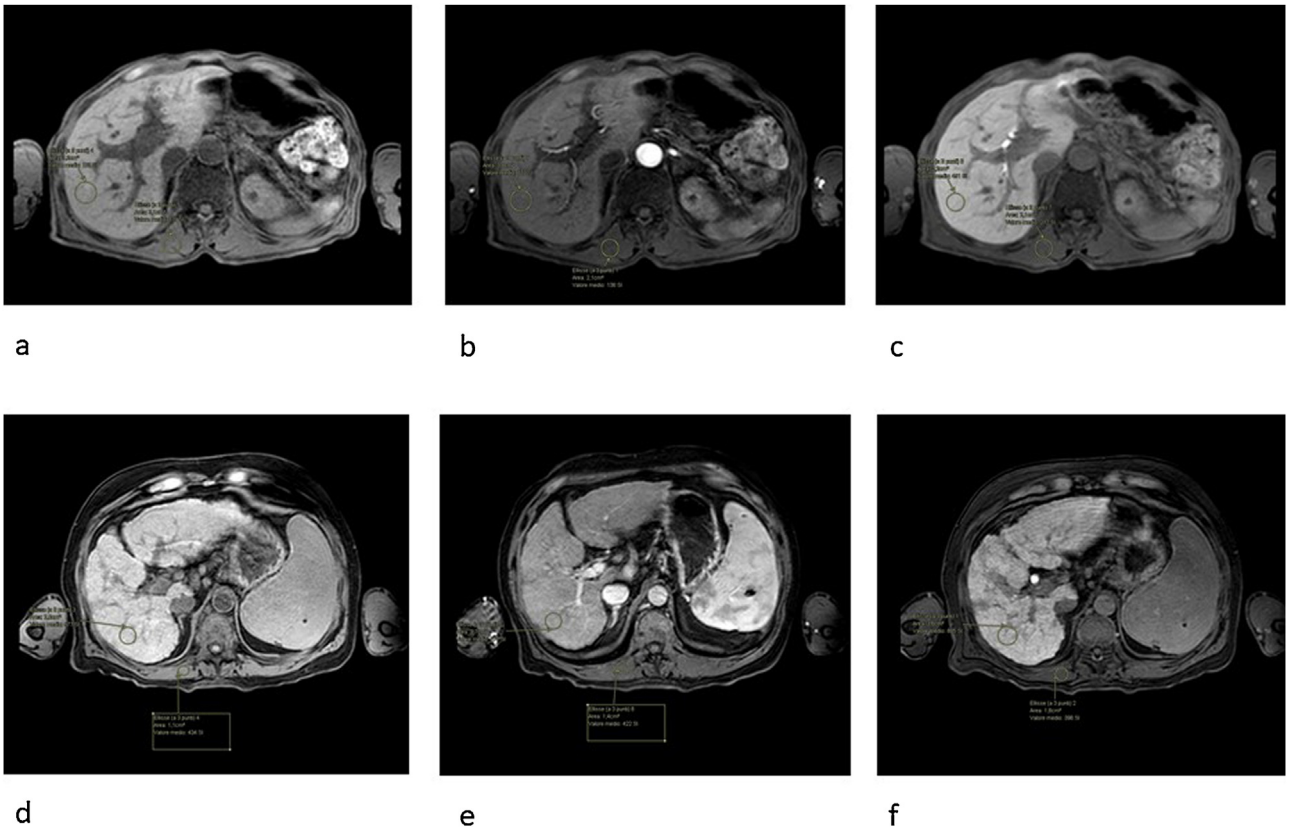

Fig. 1. Axial planes of 3D fat sat T1-weighted images before and after injection of Gd-EOB-DTPA with operator-defined region-of-interest (ROI) drawn on left liver lobe and on paravertebral muscle. Panel a–c: unenhanced, portal and hepatobiliary phase of a normal liver. Panel d–f: unenhanced, portal and hepatobiliary phase of a cirrhotic liver.

Table 2
Association between liver function and hepatobiliary and interstitial enhancement. MELD model for end stage liver disease; ALBI albumine-bilirubine; SI-HEP Signal Intensity in hepatobiliary phase; SI-POR Signal Intensity in portal phase.

Factor	Levels	N	Mean (sd)	
			SI-HEP	SI-POR
Cirrhosis	No	112	0.66 (0.40)	0.33 (0.20)
	Yes	191	0.55 (0.29)	0.35 (0.21)
	T-test p-value		0.004	0.491
CHILD grade among cirrhotics	A	153	0.59 (0.28)	0.35 (0.22)
	B	24	0.40 (0.29)	0.36 (0.21)
	C	9	0.25 (0.19)	0.38 (0.14)
	ANOVA p-value (overall)		<0.001	0.919
	Tukey HSD p-value (A vs B)		0.006	0.983
	Tukey HSD p-value (A vs C)		0.002	0.922
	Tukey HSD p-value (B vs C)		0.390	0.968
MELD among cirrhotics	≤9	92	0.61 (0.31)	0.33 (0.23)
	>9	88	0.49 (0.28)	0.38 (0.19)
	T-test p-value		0.007	0.134
ALBI grade among cirrhotics	1	75	0.50 (0.30)	0.33 (0.21)
	2	101	0.56 (0.29)	0.36 (0.21)
	3	6	0.74 (0.37)	0.37 (0.31)
	ANOVA p-value (overall)		0.105	0.529
	Tukey HSD p-value (1 vs 2)		0.378	0.517
	Tukey HSD p-value (1 vs 3)		0.139	0.877
	Tukey HSD p-value (2 vs 3)		0.321	0.995

3.3. Association between Child-Pugh score and enhancements

SI in hepatobiliary phase significantly decreases moving from Child grade A (0.59 ± 0.28) to B (0.40 ± 0.29) and C (0.25 ± 0.19). Classes B and C were not significantly different ($p = 0.39$). Again, portal enhancement did not show any difference (0.35 ± 0.22, 0.36 ± 0.21 and 0.38 ± 0.14 respectively for A, B and C, $p = 0.919$).

3.4. Association between MELD score and enhancements

SI in hepatobiliary phase decreased from MELD class ≤9 (0.61 ± 0.31) to class >9 (0.49 ± 0.28) and the difference was statistically significant ($p = 0.007$). Again, no significant difference regarding portal enhancement was observed (0.33 ± 0.23 and 0.38 ± 0.19 respectively for MELD ≤ 9 and MELD > 9, $p = 0.134$).

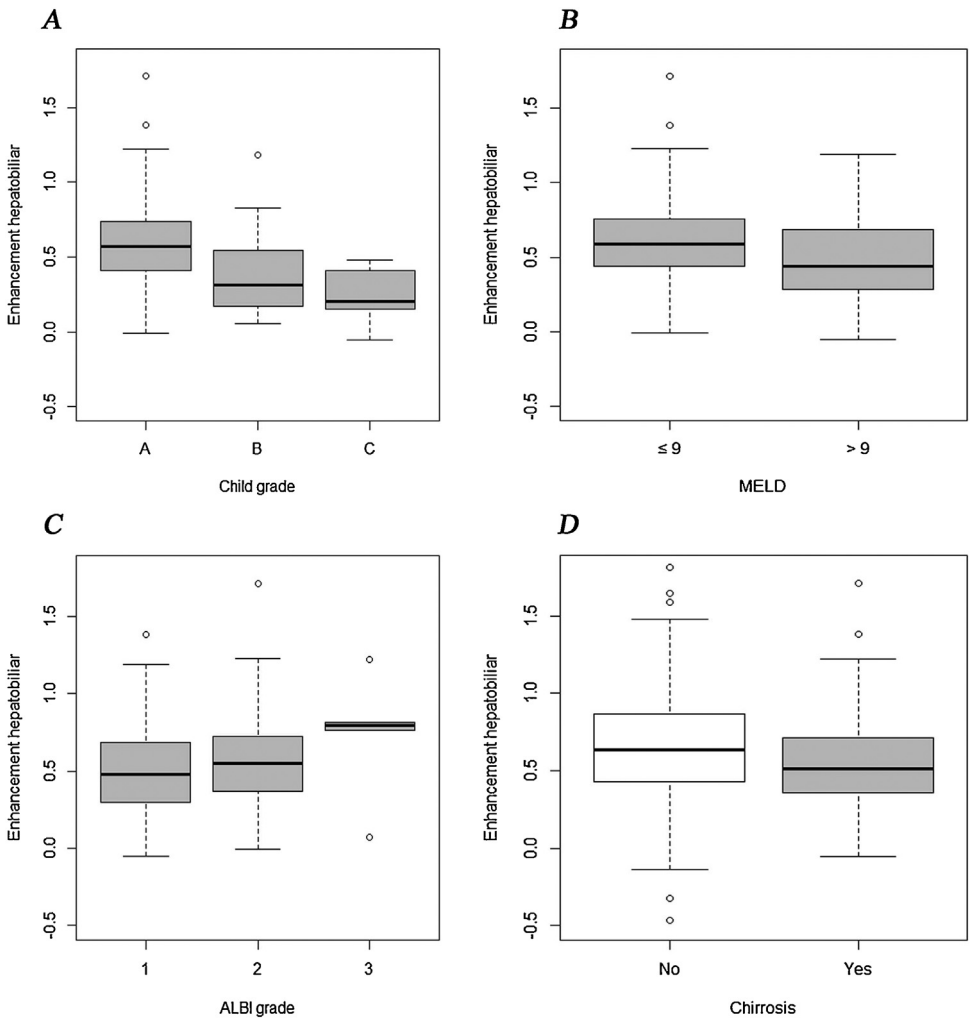

Fig. 2. Association between Child-Pugh grade (A), MELD (B) score, ALBI grade (C) and cirrhosis (D) with hepatobiliary enhancement.

When MELD was considered as a continuous variable, a weak negative correlation (rho = −0.172) was found with SI in the hepatobiliary phase.

3.5. Association between ALBI score and enhancements

SI in the hepatobiliary phase increased moving from ALBI grade 1 (0.50 ± 0.30) to 2 (0.56 ± 0.29) and 3 (0.74 ± 0.37) but the difference among groups was not statistically significant (p = 0.105). Portal enhancement was very similar among ALBI grades (0.33 ± 0.21, 0.36 ± 0.21 and 0.37 ± 0.31 respectively for 1, 2 and 3, p = 0.529).

3.6. Association between biochemical parameters and enhancements

The distribution of the biochemical parameters analyzed and the correlation with the enhancements are reported in Table 3. A negative correlation was observed between SI in hepatobiliary phase and total bilirubin (rho = −0.324) and AST (rho = −0.318) and a positive correlation with albumin (rho = 0.320), although it was moderate in either. SI in portal phase was not associated with any parameter.

3.7. ROC analysis of hepatobiliary enhancement

The ability of the hepatobiliary enhancement to classify patients according to the presence/absence of cirrhosis was moderately low (Fig. 3A), with an AUC of 0.60 (95% CI: 0.53, 0.66). However, the hepatobiliary enhancement had a good performance in the evaluation of liver function among patients with cirrhosis. In fact, the AUC index regarding the identification of patients with Child grade A vs B or C was 0.75 (95%CI: 0.66–0.83) as shown by the ROC plot of Fig. 3B. In particular, the optimal cut-off value of 0.377 had specificity, sensitivity, positive predictive value and negative predictive value respectively equal to 79.6%, 63.6%, 59.6% and 9.0%.

4. Discussion

Cirrhosis-related alterations of hepatocyte cells lead to a reduction of the uptake and excretion of gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid. In contrast to extracellular agents, approximately 50% of the injected dose undergoes specific organic anion-transporting polypeptide (OATP) 1B1/B3-dependent hepatocyte uptake and then it is excreted into the biliary system without being metabolized [11]. Contrast enhancement relies on the T1-shortening effects of the circulating gadolinium contrast agent and the T1 shortening effect is proportional to its blood concentration both in the portal phase and on its liver tissue concentration during the hepatobiliary phase [12]. In our results only

Table 3
Correlation between biochemical parameters and hepatobiliary or interstitial enhancement. SI-HEP signal intensity in hepatobiliary phase; SI-POR signal intensity in portal phase; Hb hemoglobin; WBC white blood cells; PLT platelet count; AST aspartate-transaminase; ALT alanin-transaminase; GGT gamma-glutammil-transpherase; ALP alcalyne phosphatase; PT pro-trombine time; INR international normalized ratio.

Variables	Mean (sd)	Median [IQR]	Spearman correlation (p-value)	
			SI-HEP	SI-POR
Hb	13.08 (1.97)	13.40 [12.00, 14.50]	0.166 (0.004)	0.079 (0.182)
WBC	6.13 (2.51)	5.70 [4.42, 7.10]	0.058 (0.318)	0.038 (0.521)
PLT	172.18 (84.90)	166.00 [109.75, 217.25]	0.195 (0.001)	−0.03 (0.606)
Total bilirubin	0.83 (0.58)	0.60 [0.40, 1.00]	−0.324 (<0.001)	−0.099 (0.102)
Direct bilirubin	0.69 (0.45)	0.60 [0.40, 0.80]	−0.283 (0.014)	−0.014 (0.908)
AST	37.77 (26.59)	28.00 [19.50, 47.50]	−0.318 (<0.001)	−0.019 (0.755)
ALT	34.84 (27.53)	24.50 [17.00, 44.00]	−0.209 (<0.001)	−0.044 (0.466)
GGT	68.93 (60.52)	46.50 [23.00, 97.00]	−0.213 (<0.001)	0.055 (0.376)
ALP	96.52 (47.58)	82.50 [64.25, 115.50]	−0.244 (<0.001)	−0.044 (0.482)
Sodium	140.27 (2.81)	141.00 [139.00, 142.00]	−0.029 (0.632)	−0.034 (0.574)
Total proteins	7.08 (0.83)	7.20 [6.70, 7.65]	0.04 (0.535)	0.076 (0.243)
Albumine	3.92 (0.61)	4.00 [3.60, 4.40]	0.32 (<0.001)	0.069 (0.252)
PT	1.11 (0.14)	1.08 [1.01, 1.17]	−0.208 (0.001)	0.069 (0.292)
INR	1.10 (0.14)	1.08 [1.01, 1.15]	−0.189 (0.002)	0.059 (0.341)
Creatinine	0.90 (0.26)	0.80 [0.70, 1.00]	0.04 (0.494)	0.097 (0.102)
Alpha-fetoprotein	5.52 (5.90)	3.10 [1.90, 6.20]	−0.192 (0.023)	0.003 (0.974)

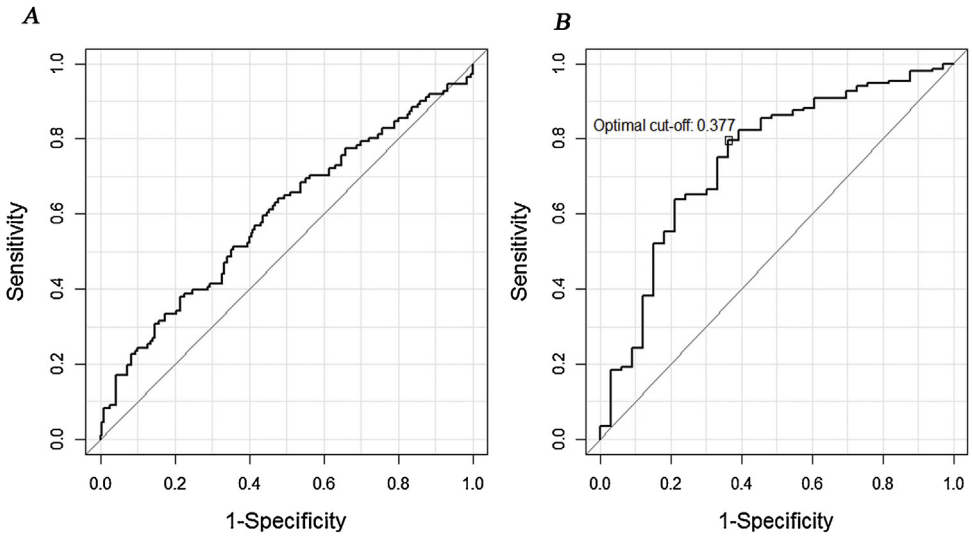

Fig. 3. ROC curves showing the performance of the enhancement hepatobiliary to identify (A) patients without cirrhosis among all patients and (B) patients with Child grade A among cirrhotic patients. Threshold for the last one is displayed.

SI-HEP was significantly reduced in cirrhotic patients when compared with non cirrhotic because this phase is an expression of hepatocyte cell function. Although portal enhancement was also reduced from an healthy to a cirrhotic liver, no association was found. Different strategies to estimate the hepatobiliary phase intensity has been described: some authors proposed to evaluate the enhancement of the biliary tract [13,14]; another study employed the quantitative liver-to-spleen ratio [15]; while others suggested to analyze the T1-relaxation time on 3T MRI [16–18]. In this study we experimented the liver-to-muscle ratio, based on the assumption that paravertebral muscles are generally considered the reference standard for the signal intensity in MRI. In addition, unlike other anatomical structures, liver and paravertebral muscles are usually located on the same imaging slice which justifies the faster ROI outlining. This easier approach does not require long training for the radiologists or sophisticated or expensive software.

Although SI-HEP showed a significant correlation with the presence of cirrhosis, in clinical practice this distinction may be useless, since cirrhosis is a dynamic disease. Child-Pugh classification is useful to stratify cirrhosis burden, and most of the previously reported techniques used to estimate SI-HEP were already significantly related to this score. To control the consistency of our new method, we have consequently first explored the potential relationship between liver-to-muscle ratio-based SI-HEP and CP score because SI-HEP is reported to progressively decrease from Child-Pugh A to Child-Pugh C [2,19]. Our results confirm this trend also in case of employing the liver-to-muscle ratio, even though the SI in hepatobiliary phase seems to reach an acceptable grade of discrimination only in dividing Child A versus the other classes. This result could be justified by the low number of patients with Child B and C in our cohort, derived from the primary-referral-center nature of our hospital, exposing the study to the risk of a type-II error. Nevertheless, this is of interest because while stage A patients usually have a well-compensated disease and good long-term prognosis, stage B and C patients are often symptomatic and complications of cirrhosis such as jaundice, ascites and systemic encephalopathy are often present. Thus, discriminating Child A patients from others is very useful, for instance, in a surgical environment, where being a well-compensated cirrhotic is a prerequisite to be a candidate for a surgical approach [20]. In this setting, MRI is often employed for diagnosis, and our results may lead in future to a whole assessment of the liver in terms of anatomy, pathology and function with

only one exam. By converse, ALBI score – recently proposed as an alternative to Child-Pugh score, and also validated as an useful tool to discriminate between survivals after liver surgery [7] – do not correlate with the radiological enhancement. To the best of our knowledge, this is the second report analyzing the correlation between liver enhancement and ALBI. The first [21] reported a strong correlation, but describing a different measurement to evaluate the SI-HEP. Thus, for this score more analysis are mandatory to explore the real ability of MRI to simulate the results of that grading. In the past years other authors tried to determine the correlation between uptake and excretion of Gd-EOB-DTPA and liver function assessed through MELD score. In particular Nilsson et al. [22], demonstrated the relationship between MRI-based liver function test and various hepatic diseases, including cirrhosis [23] and primary biliary cirrhosis [24,25]. However all these studies used in-house software to analyse the images.

Other few studies have explored the relationship between MELD score and signal intensity after Gd-EOB-DTPA injection by using indices based on operator defined region-of interest (ROI) measurements [26–28]. Those studies have employed different categorizations of MELD, supposing different cut-offs not always clearly validated in the available literature as sensible and sensitive to discriminate a pathological condition to an healthy one. Two of those studies [29,30] showed how SI-HEP would have a good discriminating power between MELD $\leqq$ 10 versus MELD > 10, a cut-off suggested to discriminate between compensated and uncompensated cirrhosis. However, this cut-off has no other validation in literature, and, to the best of our knowledge, no clear correlation with clinical significance has ever been evident. In our cohort, we focus our attention on a range recently employed by EASL to discriminate, after consensus, between a sort of healthy condition and an impaired liver function [10]. We stated a significant variation of SI-HEP when this cut-off is considered. Anyhow, in literature MELD score is often employed as a continuous variable in the clinical setting: in this case, we confirm a moderate correlation with the SI-HEP, as it was suggested by Lee et al. [31,32].

An interesting application of this results has been suggested [33] to be the segmental liver function estimation, a possible useful tool in transplantation setting, or in order to plan more or less extensive liver resections in cirrhotic livers. Thus, in future, with a sufficient follow-up period not yet reached because of the relatively new introduction of those MRI techniques, more studies may be needed to clarify if SI-HEP could be useful to discriminate more accurately different prognostic classes than the actual biochemical and clinical scores.

When biochemical assessment of liver function is considered, our data confirm the negative correlation with bilirubin and positive with albumin. These are strongly related with the impairment of the excretory and of the synthetic functions during liver damage. Thus, concerning bilirubin, an impairment of liver function led to a decrease expression of active carriers OATP 1A/3Bm which are the same carriers of Gd-EOB-DTPA. Other authors [34] recently confirmed how the enhancement could be modified with the alteration of biochemical indicators of liver functions. Our results may give other evidences on the still-now-unclear mechanism of the Gd-EOB-DTPA hepatocyte cynethic.

This study has several limitations, first of all, the retrospective data acquirement. Due to this, patients who could had been submitted to surgery were not recorded separately from the ones who had been only followed-up. This consideration did not allow to better classify the underlying liver damage, through an histological evaluation of the cirrhosis. However, clinical and diagnostic criteria were evaluated by an expert hepatologist to try reduce the effect of the absence of this information.

Secondly, we measured only SI based index and we did not take into account other indexes like T1 relaxometry, considered superior to SI by some authors [35]. Thus, in some subgroup analyses, the sample size was very small, leading to the possibility of Type-II error. Furthermore, these results had been only internally evaluated: external validation currently lacks, and it may be mandatory to confirm our associations. Lastly, even though indocyanine-green retention test seems to be the most accurate exam to evaluate liver function, we correlate the SI-HEP to indirect liver function measurement like biochemical examinations and derived score. Those types of examinations are the most diffused world-wide, so we decided to analyze parameters always available, repeatable and low-cost.

In conclusion, the SI-HEP after Gd-EOB-DTPA-enhanced MRI may be useful to evaluate and directly estimate the underlying liver function indirectly represented by Child-Pugh score and MELD score. This signal intensity directly correlates with the main liver biochemical tests, confirming the potential role for this technique as a novel radiological marker of liver function.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.04.009.

References

[1] Zeremski M, Talal AH. Noninvasive markers of hepatic fibrosis: are they ready for prime time in the management of HIV/HCV co-infected patients? J Hepatol 2005;43:2–5.
[2] Tamada T, Ito K, Higaki A, Yoshida K, Kanki A, Sato T, et al. Gd-EOB-DTPA-enhanced MR imaging: evaluation of hepatic enhancement effects in normal and cirrhotic livers. Eur J Radiol 2011;80:e311–6.
[3] Saito K, Ledsam J, Sourbron S, Otaka J. Assessing liver function using dynamic Gd-EOB-DTPA-enhanced MRI with a standard 5-phase imaging protocol. J Magn Reson Imaging 2013;37(5):1109–14.
[4] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.
[5] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.
[6] Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.
[7] Hiraoka A, Michitaka K, Kumada T, Kudo M. ALBI score as a novel tool in staging and treatment planning for hepatocellular carcinoma: advantage of ALBI grade for universal assessment of hepatic function. Liver Cancer 2017;6:377–9.
[8] Neri E, Bali MA, Ba-Ssalamah A, Boraschi P, Brancatelli G, Alves FC, et al. ESGAR consensus statement on liver MR imaging and clinical use of liver-specific contrast agents. Eur Radiol 2016;26:921–31.
[9] Okubo H, Mogami M, Ozaki Y, Igusa Y, Aoyama T, Amano M, et al. Liver function test by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging with consideration of intrahepatic regional differences. Hepatogastroenterology 2013;60:1547–51.
[10] Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[11] Seale MK, Catalano OA, Saini S, Hahn PF, Sahani DV. Hepatobiliary-specific MR contrast agents: role in imaging the liver and biliary tree. Radiographics 2009;29:1725–48.
[12] Weinmann HJ, Schuhmann-Giampieri G. A new lipophilic gadolinium chelate as a tissue-specific contrast medium for MRI. Magn Reson Med 1991;22(2):233–7.
[13] Noda Y, Goshima S, Kajita K, Kawada H, Kawai N, Koyasu H, et al. Biliary tract enhancement in gadoxetic acid-enhanced MRI correlates with liver function biomarkers. Eur J Radiol 2016;85:2001–7.
[14] Lee S, Choi D, Jeong WK. Hepatic enhancement of Gd-EOB-DTPA-enhanced 3 Tesla MR imaging: assessing severity of liver cirrhosis. J Magn Reson Imaging 2016;44:1339–45.
[15] Takatsu Y, Kobayashi S, Miyati T, Shiozaki T. Hepatobiliary phase images using gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI as an imaging surrogate for the albumin-bilirubin grading system. Eur J Radiol 2016;85:2206–10.

[16] Noda Y, Goshima S, Kajita K, Kawada H, Kawai N, Koyasu H, et al. Biliary tract enhancement in gadoxetic acid-enhanced MRI correlates with liver function biomarkers. Eur J Radiol 2016;85:2001–7.
[17] Lee S, Choi D, Jeong WK. Hepatic enhancement of Gd-EOB-DTPA-enhanced 3 Tesla MR imaging: assessing severity of liver cirrhosis. J Magn Reson Imaging 2016;44:1339–45.
[18] Zhou Z-P, Long L-L, Qiu W-J, Cheng G, Huang L-J, Yang T-F, et al. Evaluating segmental liver function using T1 mapping on Gd-EOB-DTPA-enhanced MRI with a 3.0 Tesla. BMC Med Imaging 2017;17, http://dx.doi.org/10.1186/s12880-017-0192-x.
[19] Lee S, Choi D, Jeong WK. Hepatic enhancement of Gd-EOB-DTPA-enhanced 3 Tesla MR imaging: assessing severity of liver cirrhosis. J Magn Reson Imaging 2016;44:1339–45.
[20] Llovet JM, Ducreux M, Lencioni R, Di Bisceglie AM, European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice. J Hepatol 2012.
[21] Takatsu Y, Kobayashi S, Miyati T, Shiozaki T. Hepatobiliary phase images using gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced MRI as an imaging surrogate for the albumin-bilirubin grading system. Eur J Radiol 2016;85:2206–10.
[22] Nilsson H, Blomqvist L, Douglas L, Nordell A, Janczewska I, Näslund E, et al. Gd-EOB-DTPA-enhanced MRI for the assessment of liver function and volume in liver cirrhosis. Br J Radiol 2013;86:20120653.
[23] Norén B, Forsgren MF, Dahlqvist Leinhard O, Dahlström N, Kihlberg J, Romu T, et al. Separation of advanced from mild hepatic fibrosis by quantification of the hepatobiliary uptake of Gd-EOB-DTPA. Eur Radiol 2013;23:174–81.
[24] Nilsson H, Blomqvist L, Douglas L, Nordell A, Jonas E. Assessment of liver function in primary biliary cirrhosis using Gd-EOB-DTPA-enhanced liver MRI. HPB 2010;12:567–76.
[25] Nilsson H, Blomqvist L, Douglas L, Nordell A, Jacobsson H, Hagen K, et al. Dynamic gadoxetate-enhanced MRI for the assessment of total and segmental liver function and volume in primary sclerosing cholangitis. J Magn Reson Imaging 2014;39:879–86.
[26] Lee S, Choi D, Jeong WK. Hepatic enhancement of Gd-EOB-DTPA-enhanced 3 Tesla MR imaging: assessing severity of liver cirrhosis. J Magn Reson Imaging 2016;44:1339–45.
[27] Noda Y, Goshima S, Kajita K, Kawada H, Kawai N, Koyasu H, et al. Biliary tract enhancement in gadoxetic acid-enhanced MRI correlates with liver function biomarkers. Eur J Radiol 2016;85:2001–7.
[28] Verloh N, Haimerl M, Zeman F, Schlabeck M, Barreiros A, Loss M, et al. Assessing liver function by liver enhancement during the hepatobiliary phase with Gd-EOB-DTPA-enhanced MRI at 3 Tesla. Eur Radiol 2014;24:1013–9.
[29] Verloh N, Haimerl M, Zeman F, Schlabeck M, Barreiros A, Loss M, et al. Assessing liver function by liver enhancement during the hepatobiliary phase with Gd-EOB-DTPA-enhanced MRI at 3 Tesla. Eur Radiol 2014;24:1013–9.
[30] Noda Y, Goshima S, Kajita K, Kawada H, Kawai N, Koyasu H, et al. Biliary tract enhancement in gadoxetic acid-enhanced MRI correlates with liver function biomarkers. Eur J Radiol 2016;85:2001–7.
[31] Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–6.
[32] Lee S, Choi D, Jeong WK. Hepatic enhancement of Gd-EOB-DTPA-enhanced 3 Tesla MR imaging: assessing severity of liver cirrhosis. J Magn Reson Imaging 2016;44:1339–45.
[33] Zhou Z-P, Long L-L, Qiu W-J, Cheng G, Huang L-J, Yang T-F, et al. Evaluating segmental liver function using T1 mapping on Gd-EOB-DTPA-enhanced MRI with a 3.0 Tesla. BMC Med Imaging 2017;17, http://dx.doi.org/10.1186/s12880-017-0192-x.
[34] Lee S, Choi D, Jeong WK. Hepatic enhancement of Gd-EOB-DTPA-enhanced 3 Tesla MR imaging: assessing severity of liver cirrhosis. J Magn Reson Imaging 2016;44:1339–45.
[35] Haimerl M, Verloh N, Zeman F, Fellner C, Nickel D, Lang SA, et al. Gd-EOB-DTPA-enhanced MRI for evaluation of liver function: comparison between signal-intensity-based indices and T1 relaxometry. Sci Rep 2017;7:43347.