

Original Research Article

# Hepatocyte-Specific Contrast-enhanced MRI for Quantitative Assessment of Liver Function in Children

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Abstract

**Objectives:** The liver is a complex, multifunctional organ involved in a variety of critical processes. Accurate determination of liver function in children is difficult and current biomarkers often fail to truly assess functional capacity. Advances in magnetic resonance imaging (MRI) with hepatocyte-specific, gadolinium-based agents have enabled improved liver imaging. Since a functional hepatocyte is essential for timely elimination of these agents, hepatic retention may correlate with impaired function. We aimed to determine the utility of quantitative measures of liver enhancement with contrast-enhanced MRI as a biomarker to serve as a global indicator of whole organ function in children and young adult patients with primarily pediatric pathology.

**Methods:** We performed a single-center, retrospective review of consecutive MRI examinations using gadoxetate disodium between 9/1/2010 and 9/1/2014. After exclusion criteria, 64 patient scans were analyzed and grouped according to presence (n=45) or absence (n=19) of liver disease. Quantitative enhancement measurements were performed comparing the signal intensity of the liver on the precontrast images relative to the 20 minute delayed hepatocyte phase. Specific measurements included relative liver enhancement (RLE) as well as ratios of liver enhancement compared to spleen (LSR), paraspinal muscle (LMR), and aorta (LAR).

**Results:** Mean hepatic enhancement ratios significantly differed between patients with chronic liver disease and controls without parenchymal disease (LSR  $p < 0.0001$ , LMR  $p < 0.0001$ , RLE  $p < 0.01$ ). LSR demonstrated the greatest diagnostic performance at a cutoff value of 1.65 (AUC 0.9, sensitivity 89%, specificity 84%). Furthermore, LSR ratios differentiated liver disease subpopulations from individuals without liver disease. Finally, enhancement ratios differentiated patients with normal and abnormal MELD/PELD scores.

**Conclusions:** Liver enhancement measurements on MR examinations using gadoxetate disodium in the hepatocyte phase can be used as a biomarker for identifying children with liver disease and quantifying the degree of dysfunction.

**Abbreviations:** ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUC: Area Under the Curve; INR: International Normalized Ratio; IQR: Inter-quartile Range; LAR: liver-Aorta Ratio; LMR: Liver-Muscle Ratio; LSR: Liver-Spleen Ratio; MELD: Modified End-stage Liver Disease; MRI: Magnetic Resonance Imaging; MRP2: Multidrug Resistance-associated Protein 2; NOS: Not Otherwise Specified; OATP: Organic Anion Transporting Polypeptide; PACS: Picture Archiving and Communication System; pALF: pediatric Acute Liver Failure; PELD: Pediatric End-stage Liver Disease; ROC: Receiver Operating Characteristic; RLE: Relative Liver Enhancement; ROI: Region Of Interest; TPN: Total Parenteral Nutrition;

## INTRODUCTION

The liver is a complex, multifunctional organ involved in a variety of critical processes. In children, biochemical assessment of the liver includes a number of laboratory measurements; however, the most common chemistries often fail to truly assess the hepatic functional capacity. The commonly referred to 'liver function tests' such as serum aminotransferases, alkaline phosphatase, and gamma-glutamyl transferase, do not in fact assess function and would be more appropriately termed liver enzyme tests. More apt markers of hepatic function can be broadly divided into 1) markers of synthetic capacity such as prothrombin time, international normalized ratio (INR), albumin, and the coagulation factors V and VII, 2) markers

of excretory capacity such as bilirubin and bile acids, and 3) markers of metabolic capacity such as ammonia which reflects the function of the hepatocyte-specific urea cycle proteins [1]. Clinically, the most often used markers include bilirubin, INR, and albumin. Their importance in the assessment of liver function is underscored by their inclusion into the Pediatric and Modified End-stage Liver Disease (PELD and MELD) scores [2,3]. While the scores original intent was to assess mortality while awaiting liver transplant, there exists a close relationship between mortality and function and these scores have become the most validated objective biomarkers of liver function [4]. Despite the advantages of the scoring systems, there exist around 20% of patients whose survival cannot be predicted [5]. This has led to multiple attempts at improving how best to determine overall liver function [6-8].

MRI is a common modality used to evaluate patients with various forms of liver disease. Newer gadolinium-based contrast agents, such as gadoxetate disodium (Eovist®; Bayer Schering Pharma, Berlin, Germany), are often used due to their hepatocyte-specific properties [9-11]. While most gadolinium MR contrast agents are entirely excreted by the kidneys, gadoxetate disodium has both extracellular and hepatocyte specific properties with up to 50% of the contrast agent being actively transported into the hepatocyte and excreted via the biliary system. This creates a unique hepatocyte phase of contrast enhancement that occurs approximately 20 minutes after injection in normal liver tissue [12]. Importantly, even though the contrast can also be taken up by the reticuloendothelial system of the liver, a functional hepatocyte is needed in order to excrete the injected contrast in a timely manner. Here, we aimed to determine the utility of quantitative measures of liver enhancement in the hepatocyte phase using contrast-enhanced MRI for estimating liver function in children.

## MATERIALS AND METHODS

### Study Subjects

A institutional review board-approved, HIPAA compliant, retrospective picture archiving and communication system (PACS) search was performed to identify patients who received a liver MRI examination with gadoxetate disodium (Eovist®; Bayer Schering Pharma, Berlin, Germany) from 9/1/2010 thru 9/1/2014 at our institution. Inclusion criteria consisted solely of having undergone a gadoxetate disodium-enhanced liver MRI examination. Exclusion criteria included history of liver transplant, partial hepatectomy, biliary obstruction, systemic chemotherapy, and the identification of a liver mass or vascular malformation greater than 4 cm. A cutoff of 4 cm was used so as to avoid liver mass interference with Region of Interest (ROI)-based analysis and is in line with other investigations evaluating the clinical utility of gadoxetate disodium [13-15]. Large hypervascular masses could shunt contrast away from the rest of the liver and result in low enhancement values even with normal parenchyma. Large masses could also compress the parenchyma enough that the enhancement value would be higher than it otherwise would be. ROIs were always drawn to exclude hepatic masses/nodules.

Additionally, examinations were excluded if different sequences were performed on pre- and 20 minute post-gadoxetate disodium imaging or if motion/respiratory artifact limited the accurate measurement of signal intensity values. In total, 64 examinations performed on 54 patients were selected for inclusion.

In addition to PACS search, a chart review was performed to delineate demographics and pertinent liver biochemistries (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, international normalized ratio (INR), albumin, and alkaline phosphatase) (Table 1). Biochemical markers were recorded if there was a value listed in the chart within 3 months of the MRI. When possible, a MELD (patients ≥ 12 years old) or PELD score (patients < 12 years old) was calculated.

### MR Imaging Protocol

All imaging was performed on a 1.5T system (Signa Excite HDxt; GE Healthcare, Waukesha, WI) with phased array body multicoil. Gadoxetate disodium (Eovist®; Bayer Schering Pharma, Berlin, Germany) was used as a hepatocyte contrast agent. All patients received a standard dose of 0.2 mL/kg body weight administered as a bolus injection. Only the pre- and 20 minute post-T1 weighted transverse spoiled gradient-echo sequences were evaluated (LAVA). Per standard protocol and when feasible, breath-hold technique was utilized in order to obtain optimal images. Sequence parameters varied based on body habitus. Representative parameters were repetition time (TR) 4.0ms / echo time (TE) 1.9ms, flip angle 12, field of view 26 cm, matrix 256 x 256, slice thickness 4.4 mm.

### Image Analysis

Region of interest (ROI) measurements were drawn manually and ratios were measured by a single reader on a separate workstation (VitreaAdvanced, Toshiba Medical Systems). Small liver ROIs were drawn in segments 2-8 having a mean size of 219 ± 116 pixels (range 52-572). Additionally, a single large liver ROI was also drawn through the mid portion of the liver (mean 7708 ± 3314 pixels, range 1939-14859). The inclusion of hepatic vessels within the ROI regions does have the potential to decrease overall signal intensity and alter liver enhancement values. While small vessels were incorporated into the large ROI measurements, major vessels were excluded. Importantly, although the inclusion of more hepatic vessels occurred with the large ROI assessments, we found that a single large ROI gave an equivalent value to the average of 6 individual ROI's (see Results section below). ROIs were also drawn in the spleen, paraspinal muscle, and aorta for calculation of liver-spleen (LSR), liver-muscle (LMR), and liver-aorta (LAR) enhancement ratios. Relative liver enhancement (RLE) was also calculated. The small liver ROIs were averaged (S2-8). The ratios were calculated in the following manner: LSR = (SIpost liver/SIpre liver)/(SIpost spleen/SIpre spleen), LMR = (SIpost liver/SIpre liver)/(SIpost muscle/SIpre muscle), LAR = (SIpost liver/SIpre liver)/(SIpost aorta/SIpre aorta), and RLE = (SIpost liver - SIpre liver)/(SIpre liver) [17].

### Statistical Analysis

All statistical analyses were done with SPSS Statistics (version 21, Chicago, IL). Two-sample t tests was used to assess differences in continuous variables such as those listed in Table 1. Additional analysis was used to determine if significant differences occurred in enhancement ratios of sub populations as shown in Figures 3 and 4 [18]. Bland-Altman analysis and Pearson correlation were used to determine if agreement exists between enhancement ratios performed with the average of 6 small hepatic ROIs versus 1 large ROI. A range of agreement was defined as mean percent difference ± 2 SD. Receiver operating characteristic (ROC) analyses was performed to determine optimal enhancement values separating examinations of normal from abnormal livers. All tests were two-sided and values of p < 0.05 indicated a significant difference.

## RESULTS

### Participant Characteristics

Between 9/1/2010 and 9/1/2014, 221 gadoxetate disodium-enhanced liver MRI examinations were performed at the Cincinnati Children's Hospital Medical Center. After exclusion criteria were applied, 64 patient scans performed on 54 patients were included in the study. Of the patients who received multiple scans, 6 patients received 2 MRIs and 2 patients received 3 MRIs. The average time between scans for those patients that had multiple imaging was 212.7 days. Individual lab values were recorded for each scan and were independent from each other and were therefore included as separate data entries. Patient scans were initially divided into two groups: those from patients with known liver disease (n=45; age  $13.1 \pm 9.8$ , IQR 18.2 years) and those from patients without liver disease (n=19; age  $12.1 \pm 9.5$ , IQR 11.7 years) (Table 1). Liver disease was defined as patients who fulfilled a constellation of findings that ultimately led to the assignment of ICD-9 code that constituted hepatobiliary involvement. Patients without liver disease (n=19; age  $12.1 \pm 9.5$ , IQR 11.7 years) primarily consisted of children who had an MRI performed to follow up on a suspected liver lesion identified on an alternative imaging modality, such as ultrasound or CT scan, which was not identified by MR (14/19). The remaining control population consisted of two patients with hemangioma and one each with focal nodular hyperplasia, hepatic cyst, and adenoma. Chart review in these subjects did not reveal any evidence for chronic parenchymal liver disease predisposing to a neoplasm. Scans from patients with liver disease were broadly characterized into 3 groups – 1) biliary disease (11/45; age  $5.7 \pm 4.3$ , IQR 7.9 years) such as biliary atresia and primary sclerosing cholangitis, 2) cardiac hepatopathy (9/45; age  $24 \pm 8.7$ , IQR 8.6 years) referring to patients with congenital heart disease and biochemical evidence of liver disease, abnormal liver stiffness on elastography [4,19-21], or additional abnormal liver imaging findings [22], and 3) liver disease not otherwise specified (NOS, 25/45; age  $12.5 \pm 5.2$ , IQR 5.9 years) such as glycogen storage disease, alpha-1 antitrypsin disease, and Wilson's disease.

### Biochemical Assessment of Liver Function

In addition to demographics, biochemical assessment of hepatocyte disruption and function were recorded (Table 1). Although there were some clear trends between patients with liver disease and those without, no single marker demonstrated a statistically significant difference ( $p < 0.05$ ). Importantly, markers associated with liver function such as total bilirubin, albumin, and, INR, in addition to the MELD/PELD scores, did not demonstrate significant differences between the two populations (Table 1).

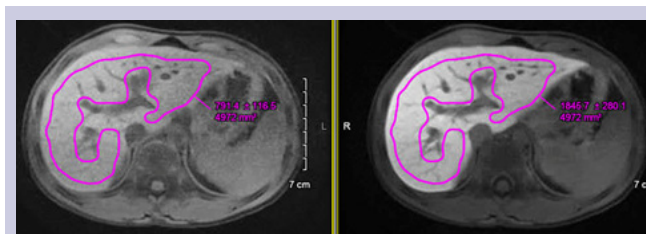
### Region of Interest (ROI) Measurements

significant linear relationship was found for all quantitative hepatic enhancement values obtained by sampling the average of 6 small ROIs in individual liver segments versus a single large ROI ( $r = 0.991-0.999$ ) (Figure 1). Bland-Altman analysis found no significant difference between 0 and the mean percent difference of the two measurement methods and no proportional

**Table 1.** Comparison of demographics and biochemical markers among 2 groups

	No Liver Disease (n=19)	Liver Disease (n=45)	p Value
Age (years)	$12.1 \pm 11.7$	$13.1 \pm 9.8$	0.67
Gender			
male	8 (42%)	17 (38%)	
female	11 (58%)	28 (62%)	
Height (cm)	$135.0 \pm 57.4$	$134.9 \pm 48.5$	0.99
Weight (kg)	$46.6 \pm 50.8$	$42.3 \pm 40.2$	0.56
ALT (IU/L)	$23 \pm 10$	$112 \pm 88$	0.06
AST (IU/L)	$28 \pm 17.5$	$137 \pm 81$	0.05
Tot Bilirubin (mg/dL)	$0.6 \pm 0.34$	$2.5 \pm 1.3$	0.15
INR	$1.03 \pm 0.1$	$1.2 \pm 0.32$	0.06
Albumin (gm/dL)	$4.0 \pm 0.8$	$3.7 \pm 1.25$	0.27
Alk Phos (IU/L)	$170.5 \pm 152.1$	$262.1 \pm 242.3$	0.06
MELD/PELD	$-1.6 \pm 14.5$	$4.5 \pm 14$	0.09
<b>ALT</b> =alanine aminotransferase; <b>AST</b> =aspartate aminotransferase; <b>INR</b> =international normalized ratio; <b>MELD</b> =Modified End-stage Liver Disease; Demographics, biochemical assessments, and calculated PELD/MELD scores for patients with and without liver disease. Biochemical markers and PELD/MELD calculation performed on data collected within a 3-month period prior to, or after obtaining of the MRI.			
<b>Abbreviations:</b> ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the curve; INR: international normalized ratio; IQR: Interquartile Range; LAR: liver-aorta ratio; LMR: liver-muscle ratio; LSR: Liver-Spleen Ratio; MELD: Modified End-stage Liver Disease; MRI: magnetic resonance imaging; MRP2: multidrug resistance-associated protein 2; NOS: not otherwise specified; OATP: organic anion transporting polypeptide; PACS: picture archiving and communication system; pALF: pediatric acute liver failure; PELD: Pediatric End-stage Liver Disease; ROC: receiver operating characteristic; RLE: relative liver enhancement; ROI: Region of Interest; TPN: total parenteral nutrition			

bias for LSR, LMR, LAR, and RE, indicating good agreement. This distinction is important as averaging multiple ROI's is more commonly used in the literature for quantitative enhancement measures [20-22]. The finding that a single large ROI gives an equivalent value to the average of 6 individual ROI's demonstrates that it is sufficient for clinical applications, dramatically decreasing the time requirement for quantitative analysis.

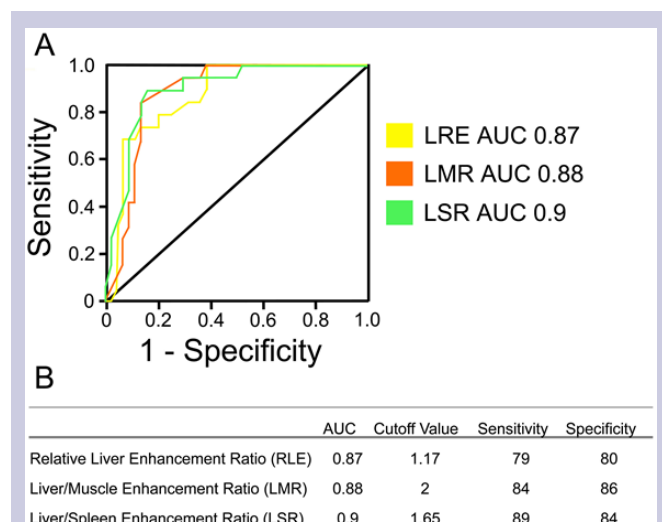


**Figure 1.** Representative image of pre- and post-contrast enhancement with single ROI measurements demonstrating increased enhancement measurement.

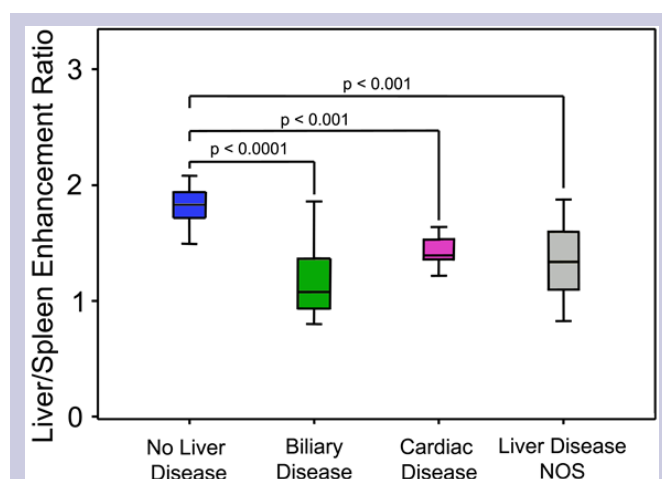
### Liver Enhancement Ratios in Patients With and Without Liver Disease<sup>3</sup>

Liver enhancement ratios for LSR ( $p < 0.0001$ ) and LMR ( $p < 0.0001$ ) in addition to the RLE ( $p < 0.01$ ) were significantly lower in patients with known liver disease compared to normal

controls. No difference was appreciated between LARs ( $p=0.075$ ). Performing receiver-operator characteristics (ROC) analyses we found that the LSR demonstrated the greatest diagnostic performance at a cutoff value of 1.65 (AUC 0.9, sensitivity 89%, specificity 84%). LMR and RLE also performed well with AUC values of 0.88 and 0.87 respectively (Figure 2). To determine the overall effect of each sub-population of patients with liver disease on the differences in enhancement, we performed individual analyses and discovered that all 3 groups of patients with liver disease had significantly lower enhancement ratios when compared to normal controls (Figure 3).



**Figure 2.** Receiver-operating characteristics (ROC) curve for enhancement ratios differentiating patients with liver disease from normal controls (A). The Liver/Spleen ratio (LSR) demonstrated the greatest diagnostic performance at a cutoff value of 1.65 (AUC 0.9, sensitivity 89%, specificity 84%). LMR and RLE also performed well with AUC values of 0.88 and 0.87 respectively (B).

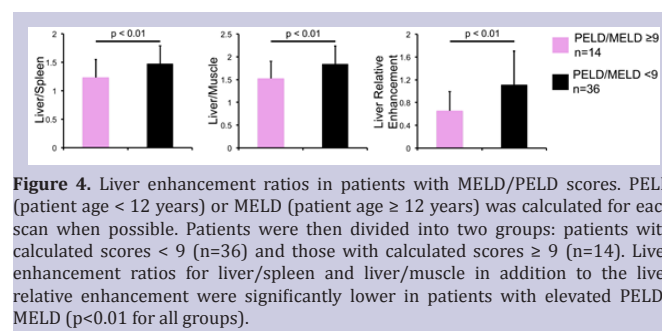


**Figure 3.** Liver/Spleen enhancement ratio (LSR) in sub-populations of patients with liver disease. Patients were sub-categorized into 3 groups - primary biliary disease (green box,  $n=11$ ), cardiac hepatopathy (purple box,  $n=9$ ), and liver disease NOS (grey box,  $n=25$ ). All subgroups had significantly lower LSR compared with normal controls (blue box,  $n=19$ ).

### Liver Enhancement Ratios in Patients with MELD/PELD Score

When possible, a PELD (patient age < 12 years) or MELD (patient age  $\geq 12$  years) was calculated that correlated with each scan. Patients were then divided into two groups: patients with

calculated scores < 9 ( $n=36$ ) and those with calculated scores  $\geq 9$  ( $n=14$ ). The decision to use 9 as the cut-off score was based on data demonstrating that patients with scores less than 9 had the lowest 3 month waiting list mortality [23]. Liver enhancement ratios for LSR and LMR in addition to the RLE were significantly lower in patients with elevated PELD/MELD scores compared to individuals with lower scores (Figure 4).



**Figure 4.** Liver enhancement ratios in patients with MELD/PELD scores. PELD (patient age < 12 years) or MELD (patient age  $\geq 12$  years) was calculated for each scan when possible. Patients were then divided into two groups: patients with calculated scores < 9 ( $n=36$ ) and those with calculated scores  $\geq 9$  ( $n=14$ ). Liver enhancement ratios for liver/spleen and liver/muscle in addition to the liver relative enhancement were significantly lower in patients with elevated PELD/MELD ( $p<0.01$  for all groups).

## DISCUSSION

The present study introduces a novel application for contrast-enhanced MRI in the assessment of liver function in children by demonstrating that children with liver disease and abnormal PELD/MELD scores have significantly lower enhancement ratios when compared to normal controls. While adult studies have previously reported the potential application of MRI imaging to determine liver function [15,17,24-26], to our knowledge, this is the first report that investigates the utility of quantitative measures of liver enhancement with contrast-enhanced MRI as a biomarker for liver function in pediatric patients with pediatric specific diseases.

Biochemical markers of liver function often fail to appropriately reflect true hepatic dysfunction. This shortfall is problematic as assessment of liver function is crucial for appropriate selection of therapeutic interventions and the allocation donor livers in patients with end-stage liver disease [23,27,28]. Furthermore, liver diseases like cardiac hepatopathies and cystic fibrosis-related liver disease may be significantly advanced before changes in liver biochemistries or synthetic markers become apparent, predisposing significant risk for decompensation secondary to liver complications. Additionally, many markers of liver function used in clinical practice, such as bilirubin, albumin, and INR, are often altered by the treatment modalities such as ursodeoxycholic acid, albumin infusions, and vitamin K. The end result of these necessary treatments is the alteration of the clinician's ability to fully assess liver function. The current studies overcame this clinical challenge by allowing direct quantification of the liver's ability to process gadoxetate disodium and demonstrated that hepatospecific MRI may very well be a single test that has the discriminatory power to differentiate children with liver disease and categorize the severity.

Gadoxetate disodium is a liver-specific contrast agent that enables hepatocyte-selective evaluation [10,11,29-31]. The transport of contrast into the hepatocyte occurs via the ATP-dependent organic anion transporting polypeptide (OATP1) and excreted via the biliary system by the multidrug resistance-



associated protein 2 (MRP2) located at the canalicular membrane [25,32-34]. Thus the liver enhancement effects are dependent on the liver's functional ability to transport and excrete the gadoxetate disodium. Normal liver parenchyma shows the strongest signal intensity 20 minutes after contrast administration [30,35]. Subsequently, measuring signal intensity and its relative enhancement, we demonstrated that differences exist in the enhancement effects 20 minutes after contrast injection in children with liver disease. Importantly, future studies will need to focus on alternative time points following contrast injection. It is known that cholestasis can affect hepatic uptake, enhancement, and excretion and future analyses will benefit from examining extended post-injection images so as to better characterize how disease-specific pathology affects the images obtained after gadoxetate disodium administration. Similar to a nuclear renogram, clinicians may one day be able to assess perfusion, function, and drainage of the hepatobiliary system in a manner akin to a renal nuclear medicine study.

Our data indicate that children with liver disease had significantly lower enhancement ratios when compared to a cohort of normal controls. These findings support a possible role for imaging in the assessment of liver function in children with known and suspected liver disease. Importantly, subgroups of patients with liver disease demonstrated universally decreased enhancement ratios compared to normal controls. As such, the use of contrast-enhanced MRI in the determination of liver function can be applied broadly to many subsets of populations with either primary or secondary hepatic dysfunction as it relates to their underlying disease. Furthermore, when we applied our approach to the highly validated PELD/MELD scoring system, we found similar results. Patients with abnormal PELD/MELD scores had significantly lower enhancement ratios compared to children with normal liver function as determined by the severity score.

Additional investigations will need to validate and appropriately context the clinical usefulness of these findings. At this time, gadoxetate disodium is not approved for the assessment of liver function but is primarily used for improved hepatic lesion characterization. While clinically intriguing, these findings do raise the question of whether patients with known liver disease should have gadoxetate disodium studies performed to better characterize identified liver lesions (its original intended purpose) as the altered background enhancement may obscure the radiographic interpretation. Regarding the clinical utility of our findings, one could envision obtaining a hepatospecific MRI in order to estimate the functional reserve in patients with chronic liver disease (i.e. cardiac disease, cystic fibrosis, or TPN associated liver disease) who are evaluated prior to major surgery (requiring cardiopulmonary bypass). Or using the findings to predict which pediatric patients with acute liver failure (pALF) have the capacity to recover versus will need a liver transplant. Finally, the reported findings could be used to potentiate the diagnosis of global hepatic dysfunction and improve the current predictive scores as it relates to mortality and organ allocation.

The findings of our study should be interpreted within the context of some methodological limitations. This was a retrospective review and as such may not have allowed for exact

comparison regarding biochemical markers of liver function and contrast-enhanced MR assessment. Regarding the study cohort, the population is notable for a disproportionate number of patients with liver disease than without. Additionally, the relatively small number of patients fulfilling criteria did not allow for specific disease-based analyses and the broad categorizations may not be truly reflective of the patient population. This is particularly pertinent as it relates to the biliary disease group as physiological conditions such as cholestasis can affect hepatic uptake and excretion. A prospective study design would clarify our observations.

## CONCLUSION

In conclusion, our findings indicate that quantitative liver enhancement values obtained from MR imaging using a hepatobiliary specific contrast agent has the potential to serve as a marker of liver function in pediatric patients. We found significant differences in multiple enhancement values between patients with and without liver disease and were able to determine highly accurate cutoff values differentiating the two groups. These findings may have broad implications for the incorporation of MRI-based analyses into future scoring and treatment algorithms to help improve the management of children with diseases of the liver.

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## DISCLOSURE

The authors report no conflicts of interest and no external sources of funding were utilized for the purposes of the research presented.

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## About the Corresponding Author

### Dr. James E. Squires

#### Summary of background:

He is a Clinical Hepatologist working in the field of pediatrics with special interests in pediatric liver diseases and pediatric liver transplant. He cares for children and families with pediatric liver disease including biliary atresia, inherited liver diseases, autoimmune hepatitis, non-alcoholic steatohepatitis, and primary sclerosing cholangitis. He is a member of the Childhood Liver Disease Research Network (ChILDRen), an NIH funded consortium working together to improve the lives of children and families dealing with rare cholestatic liver diseases. He is also a member of the Studies in Pediatric Liver Transplant (SPLIT), a multifaceted organization focused on improving outcomes for children receiving liver transplantation.

#### Current research focus:

- Collaboration with ChILDRen to determine the prevalence, and factors associated with, neurocognitive deficiencies in older children with biliary atresia alive with their native liver.
- Determining the clinical variability following partial external biliary diversion in familial intrahepatic cholestasis 1 (FIC) deficiency.

- Collaboration with Graft Injury Group Observing Long-term Outcomes (GIGOLO) to determine the incidence and associated factors of idiopathic graft fibrosis in asymptomatic pediatric liver allograft recipients.
- Determining the diagnostic and predictive capabilities of novel urine biomarkers of acute kidney injury in the peri-operative period in pediatric liver transplant.
- Ancillary study of the Pediatric Acute Liver Failure (PALF) study group to explore the clinical decision making process as it relates to liver transplantation in children with acute liver failure.
- Ancillary study to the Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) consortium exploring the prevalence and phenotypic characteristics of ulcerative colitis-associated liver disease.

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