

# Validation of functional liver imaging scores derived on gadoxetic acid-enhanced MRI in hepatocellular carcinoma patients

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## Abstract

**Background and Aim:** To investigate the correlation of the functional liver imaging scores (FLIS) and the scoring system in hepatocellular carcinoma (HCC) patients.

**Materials and Methods:** Between April 2015 and December 2022, the HCC patients who underwent gadoxetic acid-enhanced MRI were analyzed. Three parameters on hepatobiliary phase images were evaluated for FLIS: liver parenchymal enhancement, biliary excretion, and signal intensity of the portal vein. The correlation between Child-Turcotte-Pugh (CTP) classification, the albumin-bilirubin (ALBI) grade, and Fibrosis-4 (F-4) score, and FLIS were analyzed. Receiver operating characteristic curve analysis was performed to demonstrate the cut-off value of FLIS for differentiating between CTP classification and ALBI grade.

**Results:** We retrospectively analyzed 178 HCC patients (144 men, 34 women; mean age, 65.9 years). A moderate negative correlation was present between CTP classification and ALBI grade, and FLIS ( $r=-0.596$  and  $r=-0.513$ , respectively). FLIS  $\leq 3$  was determined as the most optimal criterion for differentiating CTP A or B patients from CTP C patients.

**Conclusion:** This study showed that the FLIS is a simple, non-invasive imaging marker for the assessment of liver function in HCC patients.

**Keywords:** Gadoxetic acid; hepatocellular carcinoma; liver function.

## Introduction

Chronic liver disease (CLD) or liver cirrhosis (LC) is a global health problem. It is estimated that CLD or LC leads to 2 million deaths annually.<sup>[1]</sup> Hepatocellular carcinoma (HCC) and/or hepatic failure are the main causes of morbidity and mortality in the disease.<sup>[2]</sup> Hepatic function reserve is a critical clinical marker for determining prognosis. For this purpose, several classifications and scoring systems have been developed, such as the Child-Turcotte-Pugh (CTP) classification, the albumin-bilirubin (ALBI) grade, and the Fibrosis-4 (F-4) score.<sup>[3-4]</sup>

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Imaging techniques, which have been developed and widely used in the relevant patient group, have led to the idea that liver function can be evaluated and graded with imaging findings.

Gadoxetic acid (GA)-enhanced magnetic resonance imaging (MRI) has been widely used in patients with liver disease.<sup>[5]</sup> Gadoteric acid has a unique characteristic for liver imaging; it is taken up by organic anion transporters (OAT) into hepatocytes during the hepatobiliary phase (HBP). Therefore, it has been useful in assessing hepatic function and detecting HCC in patients with CLD and LC.<sup>[6]</sup>

Previously, complex protocols such as dynamic contrast enhancement index and T1 mapping at different time points had been suggested on GA-enhanced HBP MRI to predict hepatic function reserve.<sup>[7]</sup> However, these protocols require special software and time-consuming measurements. Bastati et al.<sup>[8]</sup> developed the Functional Liver Imaging Score (FLIS), derived from the three parameters on hepatobiliary phase GA-enhanced MRI. The FLIS is a semi-quantitative assessment method based on liver parenchymal enhancement (EnQs), biliary contrast excretion (ExQs), and portal vein sign (PVsQs). The most important advantage of this measurement method is its ease of application and independence from vendors. Several studies detected a strong correlation between FLIS and the CTP classification, ALBI grade, and F-4 score in CLD and LC patients.<sup>[9-12]</sup> However, there are few studies evaluating correlations between FLIS and the scoring systems (F-4 scoring, ALBI grade, and CTP classification) in HCC patients.<sup>[13]</sup> While similar studies reported in the literature excluded HCC patients or investigated liver reserve after tumor resection, the patient group in this study consisted entirely of patients diagnosed with HCC on the basis of CLD and LC.

The purpose of this study was to investigate the correlation of the FLIS and the scoring systems in HCC patients.

## Materials and Methods

This single-center, retrospective study received approval from our Cukurova University Institutional Review Board. All protocols were performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all patients. The Cukurova University Institutional Clinical Research Ethical Committee (number 130/2023) approved this single-center observational study.

## Study Population

In this study, we conducted a search within the hospital information system for data spanning from April 2015 to December 2022. The study included patients with a tumor that was either histopathologically proven or confirmed through imaging as HCC. Inclusion criteria were defined as follows:

- (a) Obtained a GA-enhanced MRI with HBP images, and
- (b) Performed laboratory tests within 2 weeks before or after MRI.

Exclusion criteria for the study were:

- (a) Poor image quality in the HBP,
- (b) Evidence of biliary obstruction on MRI,
- (c) Acute or chronic occlusion of the main portal vein,
- (d) Presence of an infiltrative HCC pattern, and
- (e) Unavailability of clinical data (ascites and hepatic encephalopathy).

### MR Examination

In this study, dynamic MRIs were performed using a 3.0 Tesla scanner (Philips Achieva, Philips Medical Systems, Best, The Netherlands) with a 16-channel body coil. HBP was acquired at the 20<sup>th</sup> minute after injection of the contrast agent. Three-dimensional turbo-field-echo images (T1 high-resolution isotropic volume examination) were obtained with the following parameters: TR 3.4 ms, TE 1.8 ms, slice thickness 2 mm, slice spacing 2 mm, matrix size 336 × 2060, and field of view 320–380 mm. The contrast agent was injected with a 22 G intravenous catheter inserted into the antecubital vein using a power injector at a rate of 2 mL/s, with a dose of 0.025 mmol/kg. After the contrast agent injection, 20–30 mL of 0.9% saline was injected sequentially at the same rate.

### Image Analysis

MRI images were analyzed by two radiologists (F.C.P., radiologist 1, board-certified with >8 years of experience in abdominal radiology; D.O., radiologist 2, who is in the 4<sup>th</sup> year of training). The three parameters, which included EnQs, ExQs, and PVsQs, were analyzed on the hepatobiliary images by the radiologist. The parameters were scored as 0, 1, or 2. The FLIS, ranging from 0 to 6, represented the sum of the three parameters (Fig. 1, 2). The definition and grading system of the three parameters of the FLIS are presented in Table 1.

### Clinical Data, Laboratory Tests, and Scoring (The CTP classification, ALBI grade, and F-4 score)

Patient data included the following information: age, sex, clinical details (ascites and presence of hepatic encephalopathy), and serum markers (albumin, total bilirubin, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT) / international normalized ratio (INR)), which were reviewed by the radiologist. The CTP classification was determined based on clinical, laboratory test, and imaging data.<sup>[14]</sup>

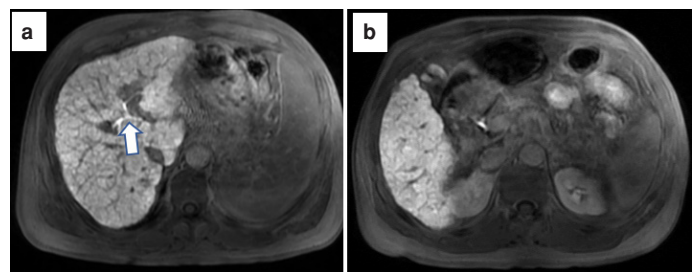
The ALBI score was determined using the following formula, which is based on serum albumin and total bilirubin levels:

$$\text{ALBI score} = (\log 10 \text{ bilirubin } [\mu\text{mol/L}] \times 0.66) + (\text{albumin } [\text{g/L}] \times -0.085).^{[15]}$$

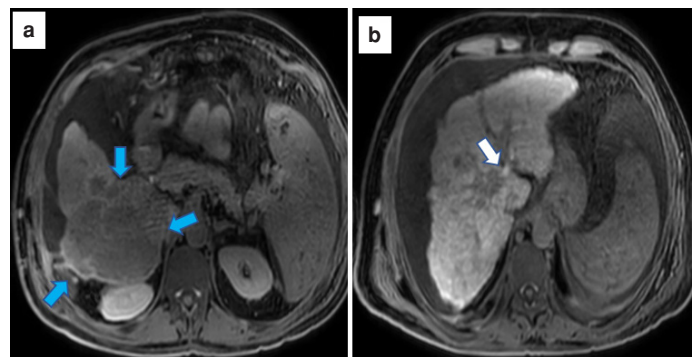
The ALBI grade was assigned based on the obtained score as follows:

- Grade 1: ALBI score  $\leq -2.60$
- Grade 2: ALBI score from  $-2.60$  to  $\leq -1.39$
- Grade 3: ALBI score  $> -1.39$

The Fibrosis-4 score was calculated using the following formula: age (years) × AST (U/L) / [PLT (10<sup>9</sup>/L) × ALT<sup>1/2</sup> (U/L)], where AST is aspartate transaminase and PLT is platelet count. On the basis of the Fibrosis score (cut-off, 1.45), patients were grouped as having non-advanced CLD (Fibrosis-4 score  $\leq 1.45$ ) and advanced CLD (Fibrosis-4 score  $> 1.45$ ).<sup>[16]</sup>



**Figure 1.** A 76-year-old female with chronic viral hepatitis and Child-Pugh A and ALBI grade 1 cirrhosis underwent gadoxetic acid-enhanced liver MRI. On hepatobiliary phase images, (a) portal vein sign score was 2 because the signal intensity of the portal vein demonstrated hypointensity relative to the hepatic parenchyma and biliary contrast excretion to the common bile duct (white arrow, score 2) and (b) liver parenchymal enhancement score was 2 because liver was hyperintense than that the right kidney was shown. The sum of three FLIS parameters was 6 in this patient.



**Figure 2.** A 66-year-old female with chronic viral hepatitis and Child-Pugh C and ALBI grade 3 cirrhosis underwent gadoxetic acid-enhanced liver MRI. On hepatobiliary phase images, (a) There was a necrotic tumour which histopathological proven hepatocellular carcinoma in the segment six of liver (A, blue arrows) and ascites. (b) Portal vein sign score was 2 because the signal intensity of the portal vein demonstrated hypointensity relative to the hepatic parenchyma and biliary contrast excretion to the peripheral bile duct (score 1) and (A) liver parenchymal enhancement score was 0 because the right kidney was hyperintense than that the liver (score 0) was shown. The sum of three FLIS parameters was 3 in this patient.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 24; IBM Corporation, Armonk, NY, USA). All parameters were tested for normality of distribution using the Kolmogorov-Smirnov test. Normally distributed quantitative data were presented as mean ± standard deviation (SD). Categorical variables are presented as numbers and percentages.

The correlation between each of the three FLIS scores and the CTP classification, ALBI grade, and F-4 score was investigated using Spearman's rank correlation coefficient. To differentiate the groups, receiver operating characteristic curve (ROC) analysis was applied to calculate the area under the curve (AUC) with the intersection point of the FLIS score and curve. Sensitivity and specificity values were also determined. The test was applied to each scoring system, including the CTP classification and ALBI grade.

To compare inter-observer and intra-observer variability of the obtained FLIS, we used Wilcoxon rank-sum tests and intra-class correlation coefficients (ICCs). ICC values were interpreted as follows:  $\leq 0.40$  to in-

**Table 1.** Definition and grading system of three parameters of FLIS

Parameters/definitions	Grading	Score	
Liver parenchymal enhancement quality score/ SI of parenchyma relative to kidney on HBP	Hypointense	0	
	Isointense	1	
	Hyperintense	2	
Biliary contrast excretion quality score/ Presence of contrast in the bile duct on HBP	No biliary contrast excretion	0	
	Excretion into peripheral IHD	1	
	Excretion into the CBD or the duodenum	2	
Portal vein sign quality score/ SI of portal vein relative to liver parenchyma on HBP	Hyperintense	0	
	Isointense	1	
	Hypointense	2	

FLIS: Functional liver imaging score; SI: Signal intensity; HBP: Hepatobiliary phase; IHD: Intrahepatic bile duct; CBD: Common hepatic bile duct.

dicate fair agreement, 0.41–0.80 indicated good, and  $\geq 0.80$  indicated excellent agreement. Statistical calculations were performed using 95% confidence intervals (CIs). A p-value of  $<0.05$  was considered statistically significant.

Results

The cohort of this study consisted of 178 patients, 144 male (80.9%) and 34 female (19.1%), with median age  $65.9 \pm 10.4$  years (range 20–92). Demographic, clinical, and laboratory data of the study are presented in Table 2.

Inter-Observer and Intra-Observer Variability for FLIS

Inter-observer variability for the intra-class correlation coefficient for EnQs, ExQs, PVsQs, and FLIS values were as follows: 0.856 (95% CI 0.767–0.889), 0.843 (95% CI 0.723–0.879), 0.855 (95% CI 0.737–0.945), and 0.823 (95% CI 0.762–0.868), respectively.

Mean intra-observer correlation coefficient for EnQs, ExQs, PVsQs, and FLIS values were as follows: 0.930 (95% CI 0.787–0.979), 0.933 (95% CI 0.825–0.979), 0.955 (95% CI 0.737–0.995), and 0.943 (95% CI 0.792–0.969), respectively.

Correlations of Three FLIS Parameters and FLIS with CTP Classification, ALBI Grade, and F-4 Score

In 178 patients, correlation analysis was performed for CTP classification, ALBI grade, and F-4 score with FLIS. A moderate negative correlation was present between CTP classification and ALBI grade with FLIS. There was no correlation between F-4 score and FLIS (Table 3).

ROC Analysis of FLIS for Stratification of CTP Classification and ALBI Grade

Two different FLIS criteria,  $FLIS \leq 3$  and  $FLIS \geq 5$ , were used for ROC analysis.  $FLIS \leq 3$  was used to differentiate CTP A or B patients from CTP C patients and ALBI grade 1 or 2 patients from ALBI grade 3 patients (Table 4).  $FLIS \geq 5$  was utilized to distinguish between CTP A patients and CTP B or C patients, as well as ALBI grade 1 patients from ALBI grade 2 or 3 patients (Table 5). The choice of  $FLIS \leq 3$  served as the optimal criterion for distinguishing between CTP A or B patients from CTP C patients. The AUC values for predicting CTP C were 0.849 (95% CI, 0.669–1.000) (Table 5).

**Table 2.** Demographic, clinical and laboratory data of the cohort

Parameters	All patients (n=178)
Age, years, Mean $\pm$ SD (Min–Max)	67 $\pm$ 10.4 (20–92)
Sex, n (%)	
Male	144 (80.9%)
Female	34 (19.1%)
Underlying disease, n (%)	
Hepatitis B virus	115 (64.6%)
Hepatitis C virus	59 (33.1%)
Alcoholism	4 (2.3%)
Laboratory test	
Albumin (g/L)	34.9 $\pm$ 5.9 (19.1–48.4)
Total bilirubin (mg/dL)	1.2 $\pm$ 1.0 (0.20–9.05)
Prothrombin time (INR)	1.18 $\pm$ 0.28 (0.86–4.08)
Platelet count (g/L)	126.6 $\pm$ 176 (27–176.7)
CTP classification, n (%)	
A	124 (69.7%)
B	46 (25.8%)
C	8 (4.5%)
ALBI grade, n (%)	
1	50 (28.1%)
2	103 (57.9%)
3	25 (14%)
F4 score, n (%)	
1	153 (86%)
2	25 (14%)

SD: Standard deviation; Min: Minimum; Max: Maximum; CTP: Child-turcotte-pugh; ALBI grade: Albumin-bilirubin grade; F4 score: Fibrosis-4 score.

Discussion

In this study, we demonstrated that in HCC patients, FLIS and its three parameters exhibit a moderate correlation with CTP score and ALBI grade. However, no significant correlation was found between the F-4 score and FLIS. The intra-observer and inter-observer variability in the intra-class correlation coefficient was consistent with excellent agreement. Additionally, the  $FLIS \leq 3$  and  $FLIS \geq 5$  criteria showed their efficacy in stratifying HCC patients according to CTP classification and ALBI grade.



**Table 3.** Correlations to CTP classification, ALBI grade and F4 score for FLIS and FLIS three parameters

Correlation	Coefficient (r)	p
CTP classification		
EnQS	-0.515	<0.001
ExQS	-0.567	<0.001
PVsQs	-0.301	<0.001
FLIS	-0.596	<0.001
ALBI grade		
EnQS	-0.485	<0.001
ExQS	-0.416	<0.001
PVsQs	-0.219	<0.001
FLIS	-0.513	<0.001
F4 score		
EnQS	0.130	0.085
ExQS	0.064	0.394
PVsQs	-0.001	0.990
FLIS	0.128	0.088

FLIS: Functional liver imaging score; CTP: Child-turcotte-pugh; ALBI grade: Albumin-bilirubin grade; F4 score: Fibrosis-4 score; EnQs: Liver parenchymal enhancement; ExQs: Biliary contrast excretion; PVsQs: Portal vein sign; \*: Spearman's Rank Correlation Coefficient was performed.

The FLIS scoring system, initially developed for CLD and LC patients by Bastati et al.,<sup>[8]</sup> is derived from the three parameters on hepatobiliary phase GA-enhanced MRI. This scoring system offers several advantages, as it is easy to apply and not dependent on specific vendors. The scoring system has been tested for CLD and LC patients to predict CTP classification, ALBI grade, and F-4 score.<sup>[8–12]</sup>

Lee et al.<sup>[9]</sup> conducted an evaluation of whether FLIS could correlate with the CTP classification in CLD and LC patients. They reported excellent inter-observer variability, which was consistent with excellent agreement (ICC=0.92–0.93). In this study, the inter-observer and intra-observer ICC were slightly lower (intra-observer ICC=0.76–0.86).<sup>[9]</sup> In the same study, HCC patients were excluded due to the potential impact of tumors on the results. However, in our clinical practice, especially in interventional oncology, many of our patients have both CLD or LC and HCC concurrently. For this reason, we decided to assess FLIS in HCC patients. Notably, in HCC patients, the occurrence of portal vein thrombus (either bland or tumor thrombus) has increased, which can affect liver parenchymal enhancement.<sup>[17]</sup> FLIS scoring may not be suitable for HCC patients with portal vein thrombus since FLIS parameters include parenchymal enhancement and portal vein signal intensity. Consequently, we excluded HCC patients with main portal vein thrombus from the study.

In this study, FLIS exhibited a moderate correlation with CTP score and ALBI grade (r=−0.596 and r=−0.513, respectively). Among the FLIS parameters, PVsQs showed a weak correlation with CTP classification and ALBI grade (r=−0.301 and r=−0.219, respectively). Aslan et al.<sup>[10]</sup> previously evaluated the potential correlation of FLIS with ALBI grade in CLD and LC patients and found a strong correlation between the three parameters of FLIS and ALBI grade (EnQs, r=−0.928; ExQs, r=−0.892; and PVsQs, r=−0.843). Lee et al.<sup>[9]</sup>

**Table 4.** The ROC curve analysis of FLIS (≤3) for stratification CTP classification (CTP A and B from CTP C) and the ALBI grade (ALBI grade 1 and 2 form ALBI grade 3)

	For CTP classification	For ALBI grade
Sensitivity (95%CI)	93.5 (87.7–96.6)	96.0 (86.5–98.9)
Specificity (95%CI)	48.1 (35.3–61.1)	25.0 (18.3–33.1)
Accuracy (95%CI)		
Positive predictive values	80.6 (73.3–86.1)	33.3 (26.1–41.4)
Negative predictive values	76.4 (60.0–87.5)	94.1 (80.9–98.3)
Positive LR (95%CI)	1.8 (1.4–2.3)	1.28 (1.1–1.4)
Negative LR (95%CI)	0.13 (0.1–0.3)	0.16 (0.04–0.6)
AUC (95%CI)	0.708 (0.635–0.774)	0.605 (0.529–0.677)

ROC: Operating characteristic curve; FLIS: Functional liver imaging score; CTP: Child-turcotte-pugh; ALBI: Albumin-bilirubin; CI: Confidence interval; LR: Likelihood ratio; AUC: Area under curved.

**Table 5.** The ROC curve analysis of FLIS (≥5) for stratification CTP classification (CTP A from CTP B or C) and the ALBI grade (ALBI grade 1 form ALBI grade 2 or 3)

	For CTP classification	For ALBI grade
Sensitivity (95%CI)	94.7 (90.2–97.1)	93.0 (88.2–95.9)
Specificity (95%CI)	75.0 (40.1–92.8)	50.0 (18.7–81.2)
Accuracy (95%CI)		
Positive predictive values	98.7 (95.6–99.6)	98.1 (94.7–99.4)
Negative predictive values	40.0 (19.8–64.2)	20.0 (07.1–45.2)
Positive LR (95%CI)	3.8 (1.14–12.5)	1.86 (0.8–4.1)
Negative LR (95%CI)	0.07 (0.03–0.14)	0.13 (0.05–0.36)
AUC (95%CI)	0.848 (0.787–0.897)	0.715 (0.642–0.780)

ROC: Operating characteristic curve; FLIS: Functional liver imaging score; CTP: Child-turcotte-pugh; ALBI: Albumin-bilirubin; CI: Confidence interval; LR: Likelihood ratio; AUC: Area under curved.

also reported a strong correlation between FLIS and hepatic function, and its ability to stratify the CTP classification. Interestingly, they found that PVsQs exhibited a strong correlation with the CTP classification, which differs from the data in our study. This disparity might be attributed to changes in portal vein and hepatic artery flow dynamics in HCC patients.<sup>[18]</sup> However, further research is needed to substantiate this hypothesis.

Lee et al.<sup>[9]</sup> demonstrated that the optimal criterion was FLIS ≥5 to predict CTP A (AUC: 0.938), and FLIS ≤3 to distinguish CTP C from CTP A and B (AUC: 0.896). They found that this criterion exhibited high sensitivity (83.7% and 81.8%, respectively) and specificity (81.8% and 92.9%, respectively). In our study, we also found that FLIS ≥5 and FLIS ≤3 can predict CTP classes effectively. However, FLIS did not perform as well in distinguishing ALBI grade.

Luo et al.<sup>[13]</sup> conducted an analysis of the FLIS ability to predict post-hepatectomy liver failure (PHLF) in HCC patients. They observed a weak correlation between FLIS and the ALBI score (r=−0.258); however, FLIS predicted PHLF on preoperative hepatobiliary phase GA-enhanced MRI (AUC: 0.752, 95% CI 0.712 to 0.789).

Another study by Pengpeng et al.<sup>[12]</sup> investigated the correlation between CTP classifications and FLIS performed on GA-enhanced MRI in 134 patients with CLD or LC. Accordingly, FLIS and the three parameters showed a strong correlation with the CTP score ( $r = -0.68, -0.60, -0.60, -0.82, -0.80$ ;  $p < 0.001$ ). ROC curve analysis showed that FLIS  $\geq 5$  was the optimal threshold to predict CTP A (sensitivity 83.7%, specificity 94.4%, and AUC 0.93). FLIS  $< 5$  was independently associated with the occurrence of first liver decompensation in patients with CTP A.

In our study, CTP classification, ALBI grade, and F-4 score evaluations, which are tests for evaluating liver function, were compared with FLIS scores separately for each patient. While similar studies excluded HCC patients from the study, our patient group consists of HCC patients who constitute an important part of the interventional oncology patient profile. In addition, it is thought that the number of 178 patients will be significant when considering the literature.

This study has some limitations. First, its retrospective nature could potentially affect patient selection. Second, we did not categorize patients based on tumor features, such as tumor volume, diameter, and lobar distribution, which could be essential for FLIS scoring. Third, our evaluation included patients with CLD and LC of different etiologies and varying degrees of inhomogeneity.

## Conclusion

In conclusion, our study demonstrated a moderate correlation of FLIS obtained from GA-enhanced MRI in HBP with CTP classification and ALBI grading in HCC patients. FLIS proved to be an accurate tool for stratifying patients according to CTP classification and ALBI grade. In addition, our study demonstrated excellent inter-reader agreement. Overall, FLIS is a simple and non-invasive imaging marker for the assessment of liver function.

**Ethics Committee Approval:** The Cukurova University Institutional Clinical Research Ethical Committee granted approval for this study (date: 04.02.2023, number: 130).

**Author Contributions:** Concept – DO, FCP; Design – DO, FCP; Supervision – HTB; Data Collection and/or Processing – DO, FCP; Literature Search – FCP; Critical Reviews – HTB.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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