Research Article
Cirrhosis and Liver Failure

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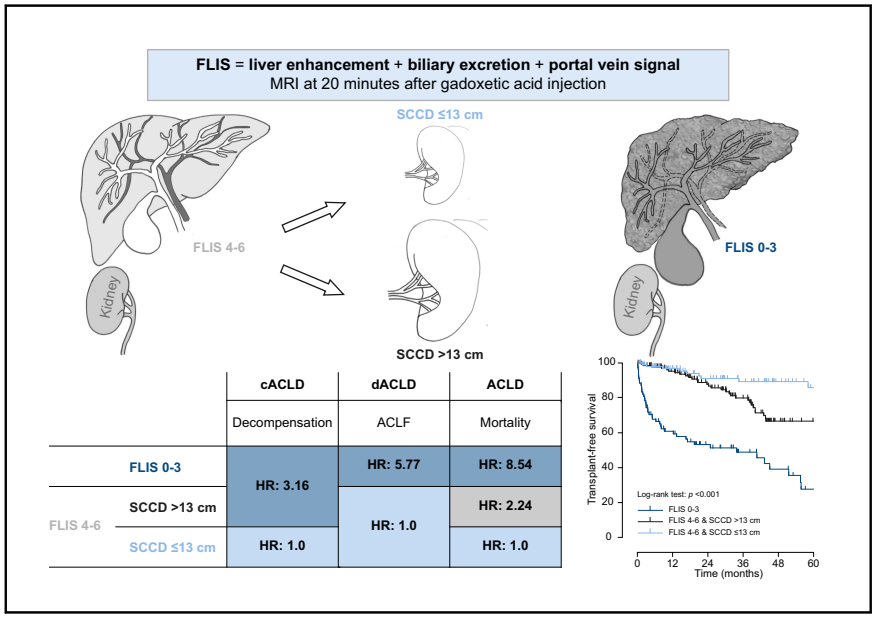
## Graphical abstract




## Highlights

- SCCD has excellent inter-reader agreement and strongly correlates with spleen volume.
- SCCD predicts hepatic decompensation in patients with compensated ACLD.
- Impaired FLIS indicates an increased risk of ACLF in patients with decompensated ACLD.
- An algorithm based on FLIS and SCCD efficiently stratifies mortality risk in patients with ACLD.

## Authors

Nina Bastati, Lucian Beer, Ahmed Ba-Ssalamah, …, Michael Trauner, Thomas Reiberger, Mattias Mandorfer

## Correspondence

ahmed.ba-ssalamah@meduniwien.ac.at (A. Ba-Ssalamah).

## Lay summary

Magnetic resonance imaging (MRI) can be used to assess the state of the liver. Previously the functional liver imaging score, which is based on MRI criteria, was developed as a measure of liver function and to predict the risk of liver-related complications or death. By combining this score with a measurement of spleen diameter, also using MRI, we generated an algorithm that could predict the risk of adverse liver-related outcomes in patients with advanced chronic liver disease.

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# Gadoxetic acid-enhanced MRI-derived functional liver imaging score (FLIS) and spleen diameter predict outcomes in ACLD

Nina Bastati[1,†], Lucian Beer[1,†], Ahmed Ba-Ssalamah[1,*], Sarah Poetter-Lang[1], Raphael Ambros[1], Antonia Kristic[1], David Lauber[1], Katharina Pomej[2,3], Teresa Binter[2,3], Benedikt Simbrunner[2,3], Georg Semmler[2,3], Lorenz Balcar[2,3], Yesim Bican[1], Jacqueline C. Hodge[1], Thomas Wrba[4], Michael Trauner[2], Thomas Reiberger[2,3], Mattias Mandorfer[2,3]

[1]*Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria;* [2]*Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria;* [3]*Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria;* [4]*IT4Science, Medical University of Vienna, Vienna, Austria*

**Background & Aims:** Functional liver imaging score (FLIS) – derived from gadoxetic acid-enhanced MRI – correlates with liver function and independently predicts liver-related mortality in patients with chronic liver disease (CLD), while splenic craniocaudal diameter (SCCD) is a marker of portal hypertension. The aim of this study was to investigate the accuracy of a combination of FLIS and SCCD for predicting hepatic decompensation, acute-on-chronic liver failure (ACLF), and mortality in patients with advanced CLD (ACLD).

**Methods:** We included 397 patients with CLD who underwent gadoxetic acid-enhanced liver MRI. The FLIS was calculated by summing the points (0-2) of 3 hepatobiliary-phase features: hepatic enhancement, biliary excretion, and portal vein signal intensity. Patients were stratified into 3 groups according to liver fibrosis severity and presence/history of hepatic decompensation: non-ACLD, compensated ACLD (cACLD), and decompensated ACLD (dACLD).

**Results:** SCCD showed excellent intra- and inter-reader agreement. Importantly, SCCD was an independent risk factor for hepatic decompensation in patients with cACLD (per cm; adjusted hazard ratio [aHR] 1.13; 95% CI 1.04-1.23; $p$ = 0.004). Patients with cACLD and a FLIS of 0-3 points and/or a SCCD of >13 cm were at increased risk of hepatic decompensation (aHR 3.07; 95% CI 1.43-6.59; $p$ = 0.004). In patients with dACLD, a FLIS of 0-3 was independently associated with an increased risk of ACLF (aHR 2.81; 95% CI 1.16-6.84; $p$ = 0.02), even after adjusting for other prognostic factors. Finally, a FLIS and SCCD-based algorithm was independently predictive of transplant-free mortality and stratified the probability of transplant-free survival (TFS) in ACLD ($p$ <0.001): FLIS 4-6 and SCCD ≤13 cm (5-year TFS of 84%) *vs.* FLIS 4-6 and SCCD >13 cm (5-year TFS of 70%) *vs.* FLIS 0-3 (5-year TFS of 24%).

**Conclusion:** The FLIS and SCCD are simple imaging markers that provide complementary information for risk stratification in patients with compensated and decompensated ACLD.

**Lay summary:** Magnetic resonance imaging (MRI) can be used to assess the state of the liver. Previously the functional liver imaging score, which is based on MRI criteria, was developed as a measure of liver function and to predict the risk of liver-related complications or death. By combining this score with a measurement of spleen diameter, also using MRI, we generated an algorithm that could predict the risk of adverse liver-related outcomes in patients with advanced chronic liver disease.



## Introduction

The prognosis of patients with chronic liver disease (CLD) is critically dependent on the occurrence of first hepatic decompensation, *i.e.* ascites, variceal bleeding, and/or hepatic encephalopathy, since these events indicate a substantial increase in the risk of mortality.[1] The subsequent development of further hepatic decompensation significantly worsens the prognosis, since patients may experience extrahepatic organ failure (*i.e.*, acute-on-chronic liver failure [ACLF]) or liver-related death, if not transplanted in a timely manner.[2] In both compensated (cACLD) and decompensated (dACLD) advanced chronic liver disease (ACLD), stratification of risk is key in identifying patients with a dismal prognosis and initiating disease-modifying treatments,[3–6] or evaluating the patient for liver transplantation.

Currently, combined clinical/laboratory parameters, such as the fibrosis-4 (FIB-4) score to screen for advanced liver fibrosis in patients with CLD[7,8] and Child-Pugh or model for end-stage liver disease (MELD) scores, among others, that subclassify ACLD by quantifying hepatic function, are used. In addition, imaging tests such as ultrasound-based elastography, CT, and MRI – all of which suffer from well-known limitations – are increasingly used in clinical practice as they confer diagnostic and prognostic

Keywords: Magnetic resonance imaging; Cirrhosis; Portal hypertension; hepatobiliary contrast agent; gadolinium methoxybenzyl DTPA.
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* Corresponding author. Address: Medical University Vienna, General Hospital of Vienna (AKH), Department of Biomedical Imaging and Image-guided Therapy, Waehringer Guertel 18-20, A-1090 Vienna, Austria; Tel.: 00431 40400 48930, fax: 00431 40400 48940.
*E-mail address:* ahmed.ba-ssalamah@meduniwien.ac.at (A. Ba-Ssalamah).
† N.B. and L.B. contributed equally to this manuscript.

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information, the latter mostly by reflecting portal hypertension, a key driver of disease progression.[9–12]

Gadoxetic acid (GA), a liver-specific MRI contrast agent, has been introduced for the diagnostic work-up of CLD and focal liver lesions.[13] The hepatic GA uptake, a reflection of liver function, correlates with CLD severity.[14,15] Recently, Bastati *et al.* developed the functional liver imaging score (FLIS) based on 3 simple visual features on GA-enhanced MRI (GA-MRI): liver enhancement; biliary excretion; and portal vein signal intensity.[16] These 3 qualitative parameters were independently associated with the probability of graft survival after orthotopic liver transplantation. Moreover, the sum of these 3 parameters, *i.e.* the FLIS, was even more strongly associated with outcome after liver transplantation.[16] Similarly, FLIS proved to be an independent risk factor for mortality in patients with cACLD and dACLD.[17] Finally, the prognostic value of FLIS was recently externally validated.[18] Of note, FLIS requires no signal intensity measurements, equations, or specific software, and is independent of MRI field-strength and vendor; thus, it can easily be implemented in clinical practice.

However, FLIS was only weakly associated with the development of first hepatic decompensation in patients with cACLD and failed to predict further decompensation(s) in patients with dACLD.[17] This may be explained by the limited association of FLIS – primarily an indicator of hepatic function[14] – with portal hypertension severity. However, the latter is the main determinant of the risk of first hepatic decompensation.[19] While an invasive measurement of the hepatic venous pressure gradient (HVPG) is the gold standard for the assessment of portal hypertension severity,[20–22] it can be estimated from spleen size,[23–26] which has previously been linked to prognosis in patients with cirrhosis.[25]

We hypothesized that the addition of splenic craniocaudal diameter (SCCD) to FLIS may enhance the non-invasive prediction of the most relevant endpoints in patients with ACLD: (i) hepatic decompensation in cACLD; (ii) ACLF in dACLD; and (iii) mortality in all patients with ACLD. Thus, a single examination, GA-MRI, could be used for the diagnostic work-up of liver nodules, as well as for risk stratification for hepatic decompensation and mortality in ACLD.

## Patients and methods

### Inclusion and exclusion criteria

Inclusion criteria were (i) GA-MRI that included 20-minute hepatobiliary-phase images using a standard examination protocol, (ii) established diagnosis of CLD, (iii) follow-up ≥90 days (including imaging and/or clinical visit), and (iv) routine laboratory tests acquired within 2 weeks of the MRI examination. Regarding (ii), all etiologies of chronic parenchymal liver disease (including patients with non-alcoholic fatty liver and cryptogenic liver fibrosis/ACLD) were considered, while patients with acute and/or vascular liver diseases were excluded.

Exclusion criteria were (i) current or prior malignancy, (ii) mechanical cholestasis, (iii) prior liver transplantation, or (iv) transjugular intrahepatic portosystemic shunt placement, (v) portal vein thrombosis, or (vi) splenectomy.

### Study population

We assessed all consecutive patients who underwent standardized GA-MRI between 2011-2015 for inclusion and exclusion criteria (n = 2,791). These criteria were met by 242 patients.[17] To further increase our sample of patients with ACLD for the purpose of the present study, we added patients who were clinically well-characterized from a database that captured all consecutive patients seen at the ACLD outpatient ward of the Department of Gastroenterology and Hepatology between 2016 and 2019, identifying those patients with ACLD who had undergone GA-MRI. These patients were considered for inclusion using the same inclusion and exclusion criteria that were applied to the 2011-2015 cohort. The final study population comprised 397 patients (see Fig. 1 for study flow-chart). Of note, 21 of these patients were previously reported in a study that did not focus on FLIS.[27]

### Clinical data

Electronic health records (in- and outpatient documentation within our center, other Viennese hospitals, as well as national health records) were reviewed by M.D., K.P., T.B., B.S., G.S., and L.Ba. under the supervision of specialists in gastroenterology/hepatology (T.R. and M.M.) with >10 years of experience. The investigators who reviewed the clinical data were blinded to imaging data.

### Staging of liver disease

Based on the FIB-4 (cut-off 1.3 based on the European Association for the Study of the Liver 2021 recommendations[8]), the HVPG (cut-off 6 mmHg), the presence of varices on endoscopy, and a history of current hepatic decompensation, patients were classified as having non-ACLD (non-ACLD; FIB-4 ≤1.3, HVPG <6 mmHg, and no varices), cACLD (FIB-4 >1.3, HVPG ≥6 mmHg, or varices), or dACLD (history of current hepatic decompensation). The following formula was used to calculate the FIB-4 score: FIB-4 = age(years)×aspartate aminotransferase(U/L)/[platelet count($10^9$/L)×alanine aminotransferase(U/L)$^{1/2}$].[28]

### Definition of evidence of CSPH

In patients with cACLD, evidence of clinically significant portal hypertension (CSPH) was defined in accordance with Baveno VI/VII recommendations[28,29] by presence of (i) varices on endoscopy and/or (ii) spontaneous portosystemic shunts (SPSS) on MRI according to Simón-Talero,[30] as well as (ii) HVPG ≥10 mmHg, and/or (iii) liver stiffness measurement by vibration-controlled transient elastography >25 kPa within 6 months of the MRI.

### Definition of hepatic decompensation, ACLF, and transplant-free survival (TFS)

Follow-up was the time between MRI and the event of interest ((i) development of hepatic decompensation, as defined by large-volume paracentesis, variceal bleeding, grade 3/4 hepatic encephalopathy, spontaneous bacterial peritonitis, or liver-related death,[19,31–33] (ii) ACLF (as diagnosed by the EF-CLIF criteria[34]), or (iii) death), or the last available information. For all analyses, patients who underwent liver transplantation were censored on the day of surgery.

### MRI protocol

A 3T MRI scan (Magnetom Trio, A Tim; Siemens Healthcare, Erlangen, Germany) was obtained using a combined 6-element, phased-array abdominal coil and a fixed spine coil. A standard dose of gadoxetic acid (0.025 mmol/kg; Primovist in Europe and Eovist in the United States; Bayer Healthcare, Berlin, Germany) was injected intravenously at a rate of 1.0 ml/s, immediately

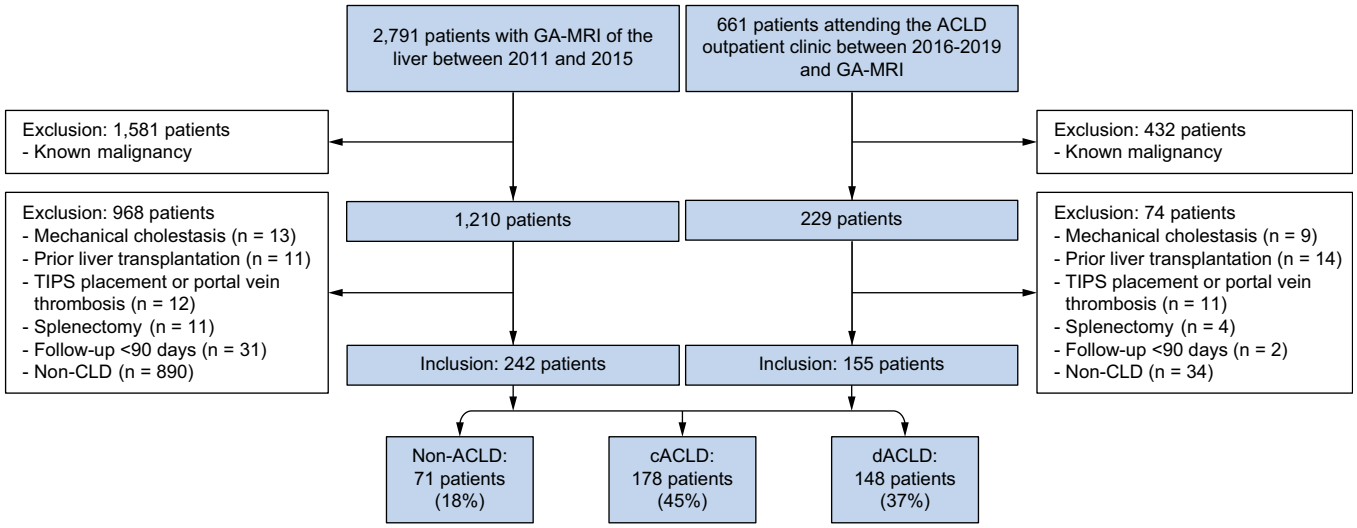


**Fig. 1. Study flow-chart showing inclusion and exclusion criteria and patient selection.**

followed by a 20 ml saline flush. Details regarding the MRI protocol are provided in the supplementary information (see Table S1).

### Image analysis

Two radiologists, one board-certified with ≥10 years of experience in abdominal imaging (radiologist 1, N.B.), one with >20 years of experience in abdominal imaging (radiologist 2, A.B.), blinded to all clinical and laboratory data, independently analyzed axial and coronal GA-enhanced MRI on a picture archiving and communication system (PACS; Impax; Agfa, Mortsel, Belgium). The coronal T2-weighted 2D- and 3D-magnetic resonance cholangiopancreatography (MRCP) as well as T2-weighted HASTE images were reviewed for bile duct dilatation as a sign of mechanical obstruction (see exclusion criteria).

In line with the previous literature,[17] FLIS was determined on axial and coronal hepatobiliary-phase scans as the sum of the enhancement quality score (EnQS; 0-2 points), the excretion quality score (ExQS; 0-2 points), and the portal vein sign quality score (PVQS; 0-2 points) (see Fig. S1). The EnQS compared the liver parenchyma to right kidney signal intensity. A score of 0 meant the liver was hypointense/darker compared to the kidney, 1 meant the liver was of equal intensity/brightness to the kidney, while 2 meant the liver was hyperintense/brighter compared to the kidney. ExQS was based on the extent of contrast opacification of the biliary tree. A score of 0 was assigned if no contrast was seen, 1 if contrast was limited to the intrahepatic bile ducts, and 2 if contrast was seen in both intrahepatic and extrahepatic bile ducts. Finally, the PVQS quality score was based on the portal vein relative to liver parenchyma signal intensity. A score of 0 meant the portal vein was hyperintense/brighter compared to the liver, 1 meant the portal vein was as intense/bright as the liver, while 2 meant the portal vein was hypointense/darker compared to the liver. Median FLIS of the 2 readers was used for the final analysis.

Volumetric assessment of the spleen was performed by radiologist 3 (L.Be. in his 5$^{th}$ year of training) using SyngoVia software (SyngoVia, Siemens Healthineers) and a semi-automatic workflow. The spleen contour was manually delineated free-hand on multiple slices in either the axial or coronal plane. After tracing the spleen contour on adjacent images, the algorithm calculated the volume by extrapolating between slices. The splenic craniocaudal, antero-posterior and medial-lateral diameters were independently assessed by radiologist N.B. and radiologist 4 (D.L. in his 5$^{th}$ year of training). Four weeks later, D.L. repeated the measurements in 41 randomly selected patients. The approximated splenic volume was calculated using the standard formula: SCCD (cm) × the antero-posterior diameter (cm) × the medial-lateral diameter (cm) × 0.52.[35]

SPSS were independently assessed by radiologists N.B. and L.Be.; in case of any disagreement, A.B. served as the judge. Patients were classified as having no SPSS,[30] small SPSS (<8 mm), or large SPSS (≥8 mm).

### Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics Version 25 (IBM, Armonk, NY) and GraphPad Prism Version 5.01 (GraphPad Software, La Jolla, CA). Continuous variables were reported as mean SD, given normally distributed data, or median (IQR), if the distribution was skewed, while categorical variables were reported as number and percentage of patients with the specific characteristics.

The Mann-Whitney *U* test was used for group comparisons of continuous variables, when applicable. Group comparisons of categorical variables were performed using the Chi-square or Fisher's exact test, as appropriate. Intra- and inter-observer variability were obtained using a mixed intraclass correlation-coefficient model, with absolute agreements, single measures, and a 95% CI. Spearman's correlation coefficient was calculated to investigate the relationship between SCCD and spleen volume. AUROC analyses were performed to investigate the discriminative ability of variables; optimal cut-off values were determined by Youden's index.[36] The associations between FLIS and SCCD, as well as prognostic algorithms derived from hepatic decompensation, ACLF development, and transplant-free mortality/survival, were investigated using Cox regression/log-rank tests, and

visualized by the Kaplan-Meier method. A $p$ value ≤.05 was considered statistically significant.

### Ethics

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and its amendments, as reflected in *a priori* approval by the institution's human research committee, which waived the requirement for written informed consent.

## Results

### Patient characteristics

We included 397 patients (246 male; 62%) with a mean age of 55 (SD ± 14) years. The most common causes of CLD were alcohol-related liver disease (97/397 [24.4%]) and viral hepatitis (HCV: 82/397 [20.7%], HBV: 30/397 [7.6%]). The most common indication for MRI was the evaluation of liver nodules (288/397; 72.5%).

Patient characteristics, including the prevalence of SPSS, were stratified by clinical stage (non-ACLD: n = 71; cACLD: n = 178; dACLD: n = 148) (see Table S2).

### SCCD increases with clinical stage and evidence of CSPH

The SCCD showed excellent inter- and intra-reader agreement, with interclass correlation coefficient values of 0.982 (range: 0.973–0.955; n = 241) and 0.997 (range: 0.994–0.998; n = 41), respectively. Notably, the SCCD was highly correlated with spleen volume (Spearman's rho = 0.887; $p$ <0.001; n = 397; Fig. S2).

There was a significant increase in the SCCD between patients with non-ACLD, cACLD, and dACLD (Kruskal-Wallis test: $p$ <0.001; Fig. 2). The proportion of patients with SCCD >13 cm increased from 33.8% in the non-ACLD group to 53.9% and 68.2% in the cACLD and dACLD groups, respectively. SCCD was higher in patients with cACLD and evidence of CSPH compared to those without CSPH (median 12.0 cm [IQR 3.2 cm] *vs.* 13.5 cm [IQR 4.7 cm]; $p$ <0.001). Comparable findings were obtained when not considering SPSS as evidence of CSPH (median 12.4 cm [IQR 3.2 cm] *vs.* 14.7 cm [IQR 4.7 cm]; $p$ <0.001).

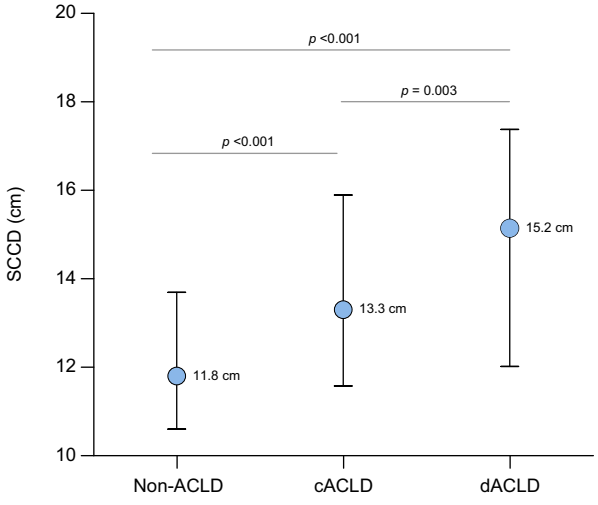


**Fig. 2. The SCCD increases with clinical stage.** The dots denote the median, while the error bars denote the interquartile ranges. Mann-Whitney *U* test. ACLD, advanced chronic liver disease; cACLD, compensated ACLD; dACLD, decompensated ACLD; SCCD, splenic craniocaudal diameter.

### Clinical outcomes

Since non-ACLD patients are at negligible risk of hepatic decompensation/death according to our previous study,[17] time-to-event analyses in the current study focused on the ACLD subgroup(s). The median follow-up among patients with ACLD was 7.5 years. Twenty-three of 326 patients (7.1%) underwent liver transplantation and 91 patients (27.9%) died. In the cACLD subgroup, 38 (21%) of 178 patients developed hepatic decompensation, while in the dACLD subgroup, 28 (20%) of 145 patients without ACLF at baseline developed ACLF.

### SCCD is a risk factor for the development of hepatic decompensation in cACLD

Interestingly, the SCCD provided a higher time-dependent AUROC for predicting first hepatic decompensation compared to other surrogates of portal hypertension, such as platelet count (PLT) or the PLT/SCCD ratio (see Table S3).

In the univariate analysis, SCCD was identified as a risk factor for hepatic decompensation in patients with cACLD (per cm; hazard ratio [HR] 1.13; 95% CI 1.04-1.20; $p$ = 0.003; Table S4). Even after adjusting for age, MELD score, and serum albumin level, the SCCD remained an independent risk factor for first hepatic decompensation (per cm; adjusted [a]HR 1.13, 95% CI 1.04-1.23; $p$ = 0.004; Table S4).

For further analyses, patients were dichotomized based on a SCCD of 13 cm, which was the optimal cut-off for predicting TFS, as determined by Youden's index. Patients with cACLD and a SCCD >13 cm (n = 96; 53.9%) were at increased risk of hepatic decompensation (HR 2.91; 95% CI 1.41-6.0; $p$ = 0.004). After adjusting for age, MELD, serum albumin levels, and the FLIS, the dichotomized SCCD remained an independent risk factor for first hepatic decompensation (aHR 2.77; 95% CI 1.31-5.85; $p$ = 0.007; Fig. S3; Table S4). Of note, the presence of SPSS was not

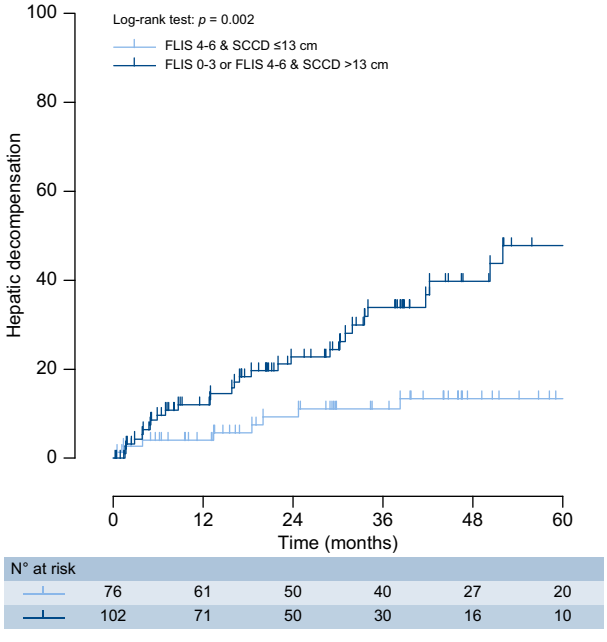


**Fig. 3. Comparison of the probability of hepatic decompensation in patients with compensated advanced chronic liver disease.** Patients were stratified by FLIS 4-6 and SSCD ≤13 cm *vs.* FLIS 4-6 and SCCD >13 cm or FLIS 0-3. The graph was truncated at 60 months follow-up. FLIS, functional liver imaging score; SCCD, splenic craniocaudal diameter.

statistically significantly associated with hepatic decompensation in patients with cACLD (Fig. S4; Table S5).

Although a FLIS of 0-3 points (previously established cut-off[17]) without a SCCD >13 cm was quite uncommon among patients with cACLD (7% of patients with a SCCD ≤13 cm), it was associated with a similarly increased risk of hepatic decompensation as in those with FLIS 4-6 points and SCCD ≤13 cm (Fig. S4). Indeed, having a FLIS of 0-3 points (aHR 3.66; 95% CI 1.16-11.51; $p$ = 0.03) was even associated with a numerically higher HR compared to FLIS 4-6 and SCCD >13 cm (aHR 2.96; 95% CI 1.35-6.5; $p$ = 0.007). Therefore, these 2 at-risk subgroups were merged into a single group of patients with cACLD at increased risk of hepatic decompensation (*i.e.*, FLIS 0-3 or FLIS 4-6 and SCCD >13 cm; Fig. 3, Table 1).

Accordingly, the combination of SCCD and FLIS enabled the detection of a larger proportion of patients with cACLD who are at increased risk of hepatic decompensation (82 out of 178 patients reclassified into the increased risk category), compared to the isolated assessment of the FLIS, thereby extending the prognostic information that can be obtained by GA-MRI.

### Patients with dACLD and a FLIS of 0-3 points are at increased risk for ACLF

Patients with dACLD and ACLF at baseline were excluded from further analysis. FLIS (0-3 *vs.* 4-6 points) was associated with the development of ACLF (HR 5.77; 95% CI 2.56-12.99; $p$ <0.001; Fig. 4; Table 2), while SCCD was not predictive, whether analyzed as a continuous (HR 0.98; 95% CI 0.89-1.07; $p$ = 0.64; Table 2) or dichotomous (HR 0.67, 95% CI 0.38-1.85; $p$ = 0.67) variable. FLIS (0-3 *vs.* 4-6 points) remained independently associated with ACLF (aHR 2.81; 95% CI 1.16-6.84; $p$ = 0.02) in patients with dACLD after adjusting for age, MELD score, and serum albumin level.

### Addition of SCCD to FLIS refines TFS prediction in ACLD

In the univariable analysis, FLIS 0-3 points (previously established cut-off[17]) was confirmed as a risk factor for transplant-free mortality in patients with ACLD (HR 5.00; 95% CI 3.28-7.63; $p$ <0.001; Table S6), while SCCD (analysed either as a continuous or dichotomous variable) showed trends, and thus, was carried forward to multivariable analysis. After adjusting for established prognostic indicators, *i.e.* clinical stage (dACLD *vs.* cACLD), age, MELD score, and serum albumin level, FLIS 0-3 points (*e.g.*, aHR 1.87; 95% CI 1.26-2.78; $p$ = 0.002) was confirmed as an independent risk factor for mortality, along with SCCD (analysed either as a continuous or dichotomous variable).

We then evaluated whether the combination of SCCD and FLIS improves the identification of patients with ACLD at increased risk for transplant-free mortality, particularly in those with preserved hepatic function (*i.e.*, FLIS of 4-6 points). Patients were allocated to the following 3 groups: (i) low-risk: FLIS 4-6 and SCCD ≤13 cm, (ii) intermediate-risk: FLIS 4-6 and SCCD >13 cm, or (iii) high-risk: FLIS 0-3 regardless of the SCCD. Indeed, there was a significant difference between the TFS of these 3 groups (log-rank test: $p$ <0.001) with median survival time being shortest for the high-risk (FLIS 0-3; 34 months; 5-year-TFS: 24%) group, followed by the intermediate-risk group (FLIS 4-6 points and SCCD >13 cm; 109 months; 5-year-TFS: 70%) (Fig. 5). Patients with a FLIS of 4-6 points and SCCD ≤13 cm (low-risk group) had the best prognosis (median survival not met; 5-year-TFS: 84%). Of note, in a *post hoc* comparison, the survival of the intermediate-risk group was significantly worse compared to low-risk patients (log-rank test: $p$ = 0.02), but better compared to the high-risk group (log-rank test: $p$ <0.001) (Fig. 5). Patients in the intermediate- and high-risk group had a more than 2- (aHR 2.33; 95% CI 1.13-4.79; $p$ = 0.02) and 4-fold (aHR 4.14; 95% CI 2.01-8.5; $p$ <0.001) increased risk of transplant-free mortality compared to low-risk patients, after adjusting for well-established prognostic indicators (Table 3).

Considerations regarding the prognostic utility of SPSS are provided in the supplementary information (Table S7; Fig. S5).

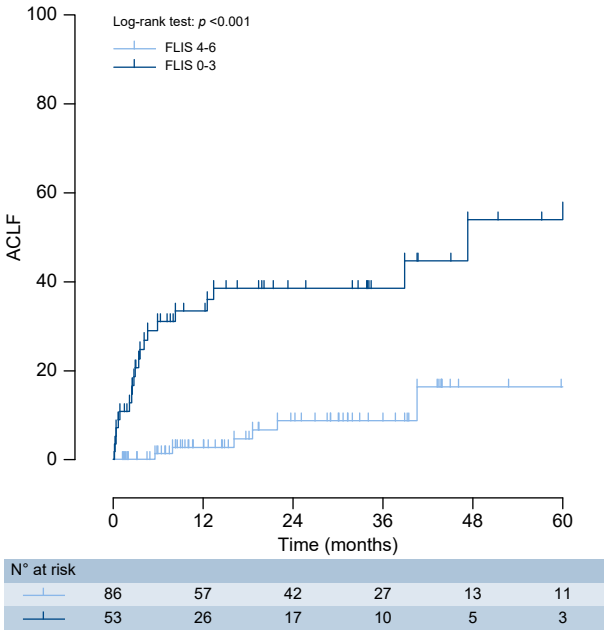


**Fig. 4. ACLF in patients with decompensated advanced chronic liver disease stratified according to their FLIS.** The graph was truncated at 60 months follow-up. ACLF, acute-on-chronic liver failure; FLIS, functional liver imaging score.

**Table 1. Uni- and multivariable Cox regression analyses on predictors of hepatic decompensation in patients with cACLD.**

| | cACLD, n = 178 | | | | | |
|---|---|---|---|---|---|---|
| | Univariable Analysis | | | Multivariable Analysis | | |
| Patient characteristics | HR | 95% CI | *p* value | aHR | 95% CI | *p* value |
| FLIS 4-6 & SCCD ≤13 cm *vs.* FLIS 4-6 & SCCD >13 cm or FLIS 0-3 | 3.16 | 1.49-6.7 | 0.003 | 3.07 | 1.43-6.59 | 0.004 |
| Age, per year | 1.01 | 0.98-1.03 | 0.65 | 1.01 | 0.98-1.04 | 0.46 |
| MELD, per point | 1.03 | 0.96-1.09 | 0.41 | 0.98 | 0.92-1.06 | 0.69 |
| Albumin, per G x $L^{-1}$ | 0.91 | 0.86-0.96 | <0.001 | 0.91 | 0.85-0.97 | 0.004 |

aHR, adjusted hazard ratio, cACLD, compensated advanced chronic liver disease; FLIS, functional liver imaging score; HR, hazard ratio; MELD, model for end-stage liver disease; SCCD, splenic craniocaudal diameter.

**Table 2. Uni- and multivariable Cox regression analyses on predictors of acute-on-chronic liver failure in decompensated advanced chronic liver disease patients.**

| | dACLD, n = 145 | | | | | |
|---|---|---|---|---|---|---|
| | Univariable Analysis | | | Multivariable Analysis | | |
| Patient characteristics | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| SCCD, per cm | 0.98 | 0.89-1.07 | 0.64 | | | |
| SCCD, >13 cm | 0.67 | 0.38-1.85 | 0.67 | | | |
| Age, per year | 1 | 0.97-1.03 | 0.97 | 1.0 | 0.98-1.04 | 0.77 |
| MELD, per point | 1.17 | 1.12-1.24 | <0.001 | 1.14 | 1.08-1.21 | <0.001 |
| Albumin, per G x $L^{-1}$ | 0.93 | 0.94-0.97 | <0.001 | 0.96 | 0.91-1.01 | 0.13 |
| FLIS, 0-3 points | 5.77 | 2.56-12.99 | <0.001 | 2.81 | 1.16-6.84 | 0.02 |

aHR, adjusted hazard ratio, dACLD, decompensated advanced chronic liver disease; FLIS, functional liver imaging score; HR, hazard ratio; MELD, model for end-stage liver disease; SCCD, splenic craniocaudal diameter.

The addition of SCCD to FLIS was also shown to refine the prediction of the composite endpoint hepatic decompensation/death in patients with ACLD. For further details please see the supplementary information (Table S8–10; Fig. S6–7).

## Discussion

Our study confirms and extends the prognostic value of GA-MRI in patients with ACLD, as it may provide information on hepatic function (FLIS) and a surrogate of portal hypertension (SCCD). Importantly, the SCCD complemented the prognostic utility of FLIS, since the SCCD predicted hepatic decompensation in patients with cACLD and expanded the at-risk population. Moreover, our study provides novel information on the prognostic ability of FLIS for ACLF in patients with dACLD and the utility of a FLIS and SCCD-based algorithm for mortality risk stratification in ACLD. Importantly, the prognostic value of GA-MRI was independent of established prognostic factors such as age, clinical stage, MELD score, and serum albumin level.

The use of imaging techniques is receiving increased attention as a method for both diagnosis and follow-up of cirrhosis and its complications. MRI, including GA-MRI, is used routinely for the diagnostic work-up of liver lesions in patients with CLD.[13] Recently, FLIS, a GA-MRI-based indicator of hepatic function, has been introduced.[16] Its 3 components, *i.e.*, hepatic GA uptake, biliary GA excretion, and the signal intensity of the portal vein, are directly related to hepatocyte function.[16] Previous publications have shown that the FLIS correlated well with liver function parameters, including the MELD and ALBI scores.[14,16] Our current study confirmed the utility of the FLIS as an imaging biomarker for mortality risk stratification. These results are in line with previous studies using FLIS, showing that this scoring system predicted re-transplant-free survival[16,37] or mortality in a previous, partly overlapping series of patients with ACLD from our center. More recently, FLIS was externally validated in an Asian cohort of predominantly hepatitis B-induced CLD,[18] an important etiology of liver-related mortality worldwide, but underrepresented in our studies due to its comparatively low prevalence in Austria. Of note, our data indicates that FLIS is a highly capable predictor of ACLF – an important clinical entity – in patients with dACLD. Since ACLF is accompanied by high short-term mortality, this finding may explain the prognostic ability of FLIS for mortality. Collectively, these data highlight the strong prognostic value of FLIS across diverse etiologies of CLD.

At specialized centers, portal hypertension can be accurately assessed by HVPG-measurement.[20,38] However, the invasiveness and limited availability of this method impede its broad clinical use, emphasizing the importance of non-invasive tests that reflect portal hypertension and facilitate risk stratification without the need for dedicated hardware/extensive expertise. Spleen volume[39,40] and length,[23] *i.e.* SCCD, have both been shown to correlate with HVPG and predict clinical outcomes in patients with CLD.[41,42] Our study showed an almost-perfect positive correlation of splenic volume and splenic length measurements. Thus, unidimensional SCCD, both practical and convenient, is a reliable substitute in clinical routine. Interestingly, SCCD was an independent risk factor for first hepatic decompensation in cACLD, as we observed a 13% increased risk of hepatic decompensation for every 1 cm increase in SCCD in adjusted analysis. This is of high clinical relevance as this event indicates a watershed moment in the natural history of ACLD as it compromises health-related quality of life and often constitutes the initiating step in a downward spiral of further decompensation, ACLF, and death.

The results of this current study indicate that the GA-MRI-derived FLIS and SCCD provide important prognostic

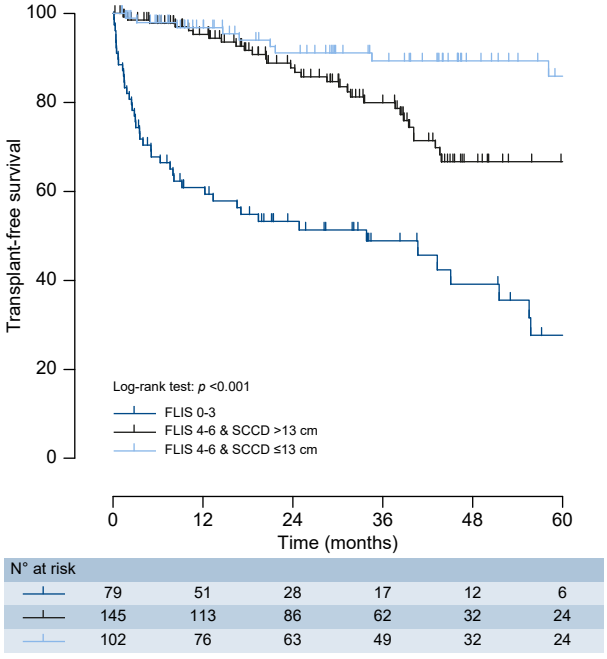


**Fig. 5. Transplant-free survival in patients with advanced chronic liver disease stratified according to their FLIS and SCCD.** The graph was truncated at 60 months follow-up. FLIS, functional liver imaging score; SCCD, splenic craniocaudal diameter.

**Table 3. Uni- and multivariable Cox regression analyses on predictors transplant-free of mortality in advanced chronic liver disease patients.**

| | ACLD, n = 326 | | | | | |
|---|---|---|---|---|---|---|
| | Univariable analysis | | | Multivariable analysis | | |
| Patient characteristics | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| FLIS 4-6 & SCCD ≤13 cm *vs.* FLIS 4-6 & SCCD >13 cm | 2.24 | 1.13-4.44 | 0.02 | 2.33 | 1.13-4.79 | 0.02 |
| FLIS 4-6 & SCCD ≤13 cm *vs.* FLIS 0-3 | 8.54 | 4.40-16.58 | <0.001 | 4.14 | 2.01-8.50 | <0.001 |
| dACLD *vs.* cACLD | 3.34 | 2.14-5.21 | <0.001 | 1.42 | 0.86-2.33 | 0.17 |
| Age, per year | 1.02 | 1.02-1.06 | <0.001 | 1.05 | 1.03-1.07 | <0.001 |
| MELD, per point | 1.13 | 1.10-1.17 | <0.001 | 1.08 | 1.04-1.11 | <0.001 |
| Albumin, per G x L-1 | 0.91 | 0.89-0.93 | <0.001 | 0.93 | 0.90-0.97 | <0.001 |

ACLD, advanced chronic liver disease; aHR, adjusted hazard ratio; FLIS, functional liver imaging score; HR, hazard ratio; MELD, model for end-stage liver disease; SCCD, splenic craniocaudal diameter.

information. Although both biomarkers are somewhat interrelated (since portal hypertension is accompanied by impaired hepatic function – and *vice versa*), splenic metrics seem particularly important in early ACLD, before the development of severe hepatic impairment. This consideration is supported by the ability of SCCD to sub-stratify risk in patients with a favorable FLIS, which led to a reclassification of a considerable proportion of "low-risk" patients according to our previous algorithm – which was solely based on FLIS – to "intermediate-risk."

Importantly, the application of FLIS and SCCD for risk stratification in non-ACLD patients is futile since they are at negligible risk of hepatic decompensation/death.

Based on the findings of our study, we have developed simple algorithms for stratifying the risks of the most relevant clinical endpoints throughout clinical stages. cACLD patients with a FLIS of 0-3 points (relatively uncommon in cACLD) and/or a SCCD of >13 cm (common in cACLD) are at an approximately 3-fold increased risk of hepatic decompensation. In patients with dACLD, a FLIS of 0-3 points is associated with an approximately 6-fold increased risk of ACLF. Finally, an algorithm based on FLIS and SCCD stratifies the probability of TFS/mortality: Patients with a FLIS of 4-6 points and a SCCD of ≤13 cm had a 5-year TFS of 84%, while there was a stepwise worsening of prognosis in those with a FLIS of 4-6 points and SCCD of >13 cm (approximately 4-fold increased risk of death; 5-year TFS: 70%) and those with a FLIS of 0-3 points (nearly 9-fold increased risk of death; 5-year TFS: 24%).

Moreover, the combination of FLIS and SSCD provided accurate information on the risk of the composite endpoint hepatic decompensation/death in ACLD and in the subgroup of patients with cACLD, solely based on radiological information.

We have to acknowledge several limitations. The retrospective design/use of real-life data may have caused selection bias due to the GA-MRI eligibility requirement. However, because GA-MRI is broadly used for the diagnostic work-up of liver nodules in patients with CLD at our institution, a bias seems less likely. As we excluded all patients with mechanical cholestasis, our findings cannot be extrapolated to this specific patient population. Moreover, external validation of our findings would be desirable. Although FLIS has already undergone external validation,[18] we are not aware of another GA-MRI cohort that has provided a similarly large number of patient years/events for adequate external validation. Also, inclusion of a broad spectrum of CLD etiologies in this cross-sectional study might have affected the results in individual etiologies; however, it also increases the generalizability of our study. Another potential drawback was the lack of histologic proof of the etiology of CLD/ACLD in some patients; nevertheless, this reflects current clinical practice, as liver biopsy is less commonly indicated due to important advances in the field of non-invasive tests.[7] Third, HVPG and liver stiffness measurement – well-established invasive and non-invasive tests for staging and prognostication[43] – were not systematically performed in these patients. Thus, we have introduced the term "evidence of CSPH" to subclassify patients with cACLD and demonstrate the relationship between SCCD and portal hypertension. In line with Baveno VII recommendations,[29] this term comprised varices on endoscopy, HVPG ≥10 mmHg, and/or LSM >25 kPa. According to Baveno VI, SPSS are indicative of CSPH. However, although we adhered to the methodology of the seminal multicenter study by Simón-Talero *et al.*,[30] we observed a surprisingly high prevalence of SPSS in the cACLD subgroup. A major difference is that we exclusively relied on MRI, while approximately 94% of patients in the study by Simón-Talero and colleagues underwent CT examination. MRI is expected to have a lower accuracy for diagnosing SPSS, due to the larger slice thickness. We hypothesize that radiologists' awareness of the methodological limitations of MRI may have lowered their threshold for diagnosing SPSS, resulting in an over-diagnosis, compared to CT. Thus, we have also provided data on evidence of CSPH with or without consideration of SPSS. Moreover, the findings of our study regarding the prognostic value of SPSS (see supplementary information) should not be overinterpreted, while further attempts to standardize imaging approaches for the detection of SPSS are needed.

Importantly, our study also has major strengths, which include the large cohort size (n = 397; n = 326 with ACLD) and a long duration of clinical follow-up (ACLD: median 7.5 years). Moreover, our analysis was stratified by the stage of underlying liver disease, excluding patients in whom advanced liver fibrosis can be ruled-out by FIB-4, and thus, are at negligible risk for liver-related events from outcome analyses. This is particularly important, as inclusion of such easy-to-classify patients who do not belong to the target population of a non-invasive test that is primarily used for prognostication in ACLD may lead to an overestimation of its prognostic value, as compared to its intended clinical application.[9]

In conclusion, the present study confirms and extends the prognostic value of GA-MRI in patients with ACLD by demonstrating the complementary information of FLIS and splenic metrics for stratifying the risks of hepatic decompensation, ACLF,

and mortality. Finally, it provides simple, easily applicable algorithms that – after validation – may introduce GA-MRI-based risk stratification into the work-up of patients with ACLD.

**Abbreviations**

ACLF, acute-on-chronic liver failure; cACLD, compensated advanced chronic liver disease; CLD, chronic liver disease; dACLD, decompensated advanced chronic liver disease; EnQS, enhancement quality score; ExQS, excretion quality score; PVQS, portal vein sign quality score; FLIS, functional liver imaging score; GA-MRI, gadoxetic acid-enhanced MRI; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; PLT, platelet count; RLE, relative liver enhancement; SCCD, splenic craniocaudal diameter; SPSS, spontaneous portosystemic shunt; TFS, transplant-free survival.

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## Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

N.B., L.Be., A.B., S.P.-L, R.A., A.K., D.L., K.P., T.B., B.S., G.S., L.Ba., Y.B., T.W., M.T., T.R., and M.M. (acquisition of data and critical revision of the manuscript); N.B., L.Be., A.B, and M.M. (study concept and design, analysis, and interpretation of data, statistical analysis, drafting of the manuscript); J.H. (critical revision of manuscript); all authors approved the final manuscript.

## Data availability statement

The data that support the findings of this study are available from the corresponding author A.B.-S. upon reasonable request and approval of the data clearing house of the Medical University of Vienna.

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## Supplementary data

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*Author names in bold designate shared co-first authorship*

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