BMJ Open

Does the change in Liver Frailty Index over the first week of hospitalisation predict mortality in patients with acute-on-chronic liver failure? A prospective cohort study from a Slovak liver centre

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To cite: Skladaný Ľ, Líška D, Mesiková K, *et al*. Does the change in Liver Frailty Index over the first week of hospitalisation predict mortality in patients with acute-on-chronic liver failure? A prospective cohort study from a Slovak liver centre. *BMJ Open* 2025;**15**:e100171. doi:10.1136/bmjopen-2025-100171

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-100171).

Received 04 February 2025
Accepted 09 May 2025

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ABSTRACT

Objective Hospital admissions for advanced chronic liver disease (ACLD) are associated with increased mortality, disability, a decline in quality of life and significant economic costs. Being admitted to the hospital usually indicates a triggering event that disrupted a previously stable condition, leading to decompensation or complications of ACLD. The most acute and severe manifestation of this imbalance is acute-on-chronic liver failure (ACLF), a syndrome representing a critical juncture. Reliable prognostic stratification of patients admitted with ACLF could facilitate the systematic delivery of tailored care, ranging from palliative care to intensive interventions like extracorporeal liver support devices and prioritised liver transplantation. Disease-specific prognostic tools, such as the Model for End-Stage Liver Disease score, are effective but have limitations, particularly in reflecting a patient's potential for recovery. The concept of the body's functional reserve in the context of ACLD/ACLF is gaining attention, with the Liver Frailty Index (LFI) potentially emerging as a recommended diagnostic tool.

Methods Patients were selected from our cirrhosis registry (RH7). The LFI serves as an indicator of the patient's prognosis. The LFI measurement takes place at two time intervals: on the patient's admission and after 7 days of hospitalisation.

Results Our RH7 registry included 154 patients (15.1%) who were diagnosed with ACLF. The primary cause of the underlying ACLD was alcohol-associated liver disease in the majority (79.8%) of cases. The mean value of LFI at admission was 4.50 (± 0.94). When patients with liver cirrhosis were categorised into three subgroups based on the LFI on day 7, survival exhibited a statistically significant decrease ($p \leq 0.05$) across all three ACLF grades. This decline in survival was observed from the 'improved LFI' cohort, through the 'stable LFI' group, to the 'worsened LFI' group.

Conclusion The impact of day 7 LFI on the survival of patients with ACLF is notable. Nevertheless, it does not markedly enhance the predictive capability of the LFI assessed on admission. Consequently, the initial LFI on day 1 continues to be the most valuable and commonly used instrument for promptly recognising individuals with ACLF.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study used a large, prospectively maintained national registry of patients with advanced chronic liver disease.
⇒ Liver Frailty Index was assessed using a standardised and validated index at two defined time points during hospitalisation.
⇒ Patients were enrolled based on strict inclusion and exclusion criteria, enhancing internal validity.
⇒ All diagnoses and clinical classifications were performed using standardised protocols and validated scoring systems.
⇒ The single-centre design may limit the generalisability of findings to broader populations or different healthcare settings.

INTRODUCTION

Advanced chronic liver disease (ACLD), preferred over 'cirrhosis', refers to structural and functional liver changes caused by inflammation, necrosis, fibrosis and vascular disruption, leading to portal hypertension and reduced liver function.[1–5] Chronic liver disease is a disease with an increased risk of mortality, reduced quality of life, increased disability and a significant economic impact.[6] Liver cirrhosis is a significant problem in Slovakia compared with all countries in the world.[1] As ACLD progresses, the availability of lifesaving conservative treatment options decreases. In cases of end-stage liver disease (ESLD), liver transplantation (LT) may be the only remaining alternative.[7 8] During the transition from ACLD to ESLD, many patients eligible for liver transplant may become too

frail or lack the reserves needed to benefit, making them too sick for the procedure.[9] The transition from ACLD to ESLD can be suddenly disrupted by acute events (triggers like infection or bleeding), leading to a complex syndrome called acute-on-chronic liver failure (ACLF).[9–11] This event significantly raises the risk of mortality within a matter of weeks.[12] Prognostic stratification is key in managing chronic and ACLF. It should assess liver function, recovery potential, mental state, health literacy, will to live and social factors. Based on this, patients fall into three groups: (1) terminal liver failure with recovery potential, (2) recovery possible for both liver and body or (3) no recovery potential. Treatment options align as liver transplant, intensive care or palliative care. Liver-specific prognostic systems like the Child-Pugh score (CPS), the Model for ESLD (MELD) and the liver-modified Sequential Organ Failure Assessment (SOFA) score for ACLF focus primarily on liver-related prognosis. This focus on the liver has led hepatology to explore additional prognostic tools aimed at assessing the functional reserve of the whole body beyond the liver.[13–17]

Frailty, reflecting the body's functional reserve, originated in geriatrics but has proven valuable in hepatology. It enhances understanding of ACLD, allows personalised prognostic stratification and reveals new therapeutic targets.[18–21] This condition stems from the cumulative impact of impairments across multiple physiological systems over time.[22–26] Frailty examination is widely used in medicine in the elderly and can be characterised as a clinical state of reduced physiological reserve and increased vulnerability to external stressors.[21 27] In patients with cirrhosis, frailty manifests as a diminished physical capacity.[28–35] Frailty is the ultimate manifestation of chronic malnutrition and loss of muscle mass. Frailty can be measured using several cognitive and physical tests.[31] Loss of muscle mass (sarcopenia) is among the basic components of frailty in patients with liver cirrhosis.[36 37] Sarcopenia is traditionally defined as a biological process of ageing.[38] Sarcopenia, frailty and cirrhosis are closely linked and strongly affect outcomes in chronic liver disease, making their understanding key to effective management.[39] The Liver Frailty Index (LFI) is the key marker of frailty in cirrhosis, assessing functional status. It predicts outcomes like longer hospital stays post-transplant, infections and poor healing.

The current literature does not include enough information on whether improving frailty during hospitalisation will lead to improved patient prognosis. The primary objectives of this study were to assess the LFI in patients with ACLF and investigate if significant differences in LFI exist: (a) across different grades of ACLF, (b) between ACLD and ACLF and (2) to evaluate whether dual measurements of LFI offer superior mortality prediction compared with a single measurement taken at admission.

MATERIALS AND METHODS

Patients were enrolled in the registry known as RH7, a registration system in Slovakia for all consenting adult patients hospitalised with ACLD/decompensated ACLD. Established in 2014, the RH7 registry is used by the Department of Hepatology, Gastroenterology, and Transplantation at the II. Internal Clinic of the Slovak Medical University (HEGITO). For this study, new patients in RH7 without contraindications to LT were chosen. Participation required patients to provide their agreement and sign an informed consent. The study included only active patients registered in RH7 who had signed the informed consent. The study excluded patients with malignancies, except for those with hepatocellular carcinoma who were within the Milan criteria; patients with acute or chronic failure of extrahepatic organs, except for those with ACLF; patients who withdrew their informed consent; and patients from whom we could not collect the required recorded variables during the 1-year follow-up period. Demographic, clinical, anthropometric and laboratory parameters were collected to determine the aetiology and stage of ACLD and ACLF. This included assessing the presence of frailty using the LFI and tracking outcomes at 28 days and 90 days, as well as at 1 year (table 1).

The study protocol (NCT04767945) was in accordance with the ethical guidelines of the Declaration of Helsinki. Ethical approval was given by the ethics committee of the Roosevelt Hospital in Banská Bystrica under number 15072. None of the patients were institutionalised. Patients and members of the public were not involved in the design, conduct, reporting or dissemination plans of this research.

The sample

The primary cohort comprised patients with ACLD who were admitted to the HEGITO Liver and Transplant Unit at the F.D. Roosevelt Teaching Hospital in Banska Bystrica, Slovakia. At the start of the study, the register RH7 database included 1023 patients, of whom 154 had ACLF and 869 did not. The presence of ACLF, along with its severity grades 1-2-3, was meticulously verified according to the study protocol by one investigator. The underlying causes of liver disease were classified into several categories: alcohol-associated liver disease (ALD), metabolic dysfunction-associated steatotic liver disease, autoimmune/cholestatic syndromes, including autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis, viral hepatitis (chronic hepatitis C and chronic hepatitis B) and others (such as cryptogenic causes, alpha-1-antitrypsin deficiency, Wilson's disease, haemochromatosis, etc). The diagnosis of ACLD was based on a set of standard criteria, incorporating clinical signs (such as variceal bleeding, cirrhotic ascites and hepatic encephalopathy), laboratory tests (Fibrosis-4, MELD, CPSs), imaging studies (upper Gastrointestinal endoscopy, abdominal ultrasound, transient elastography, CT, and MRI including elastography), liver biopsy and hepatic venous pressure gradient measurement. For all

Table 1 Baseline characteristics of the group

	Registry	ACLF				Non-ACLF
		All	1	2	3	
Count	1023 (100%)	154 (15.1%)	92 (8.99%)	48 (4.69)	14 (1.37)	869 (84.9%)
Women	404 (39.49%)	51 (4.99%)	29 (2.83%)	16 (1.56%)	6 (0.59 %)	353 (34.51%)
Men	619 (60.51%)	103 (10.07%)	63 (6.16%)	32 (3.13%)	8 (0.78 %)	516 (50.43%)
Age in years	58 (± 12)	58 (± 12)	58 (± 12.06)	58 (± 12.17)	57 (± 11.94)	57 (± 10)
Aetiology	ALD – 67.8% HCV – 4.9% HBV – 2.5% NASH – 14.9% Cryptogenic – 3.6% PSC – 4% PBC – 3.8% AIH – 2.5% (4% patients=combination)	ALD – 79.8% HCV – 3.5% HBV – 2.3% NASH – 11.4% Cryptogenic – 2.5% PSC – 3.5% PBC – 1.8% AIH – 1.8% (4.8% patients=combination)	ALD – 87% HCV – 1.1% HBV – 3.3% NASH – 15.2% Cryptogenic – 3.3% PSC – 2.2% AIH – 1.1% (13.2% patients=combination)	ALD – 85.4% HBV – 2.1% NASH – 6.3% Cryptogenic – 4.2% PSC – 4.2% (2.2% patients=combination)	ALD – 100% NASH – 7.1% (7.1% patients=combination)	ALD – 59.6% HCV – 5.7% HBV – 2.7% NASH – 17.1% Cryptogenic – 4.3% PSC – 4.5% PBC – 5.3% AIH – 3% (2.2% patients=combination)
Trigger AD	X	AAH – 45.2% Abscess – 0.5% Bacteraemia – 0.5% Bronchopneumonia – 4% *Clostridium* Colitis – 0.25% Dehydration – 0.5% DILI – 2.5% Diuretics – 1.5% Febrility – 0.25% HAV/HBV/HCV/HEV – 2.5% Inflammation – 4.3% Infection – 5.8% Bleeding – 15.9% Nef. TIPS – 0.25% SBP – 8.1% Unknown – 6.8% Soor oesophagus – 0.5% Soft tissue – 0.25%	AAH – 48.9% SBP – 13% Unknown – 9.8 % Bleeding – 8.7 % Infection – 5.4 % Others – 14.2 %	AAH – 70.8% SBP – 4.2% Unknown – 2% Bleeding – 2% Infection – 2% Inflammation – 4.2% Others – 14.8%	AAH – 71.4% SBP – 7.1% Infection – 7.1% Bleeding – 7.1% Unknown – 7.1% Others – 0.2%	X
MELD	17.32 (± 7.66)	21.29 (± 8.49)	21.32 (± 8.5)	21.25 (± 8.54)	21.42 (± 7.7)	17.32 (± 7.7)
LFI D1	4.49 (± 0.94)	4.50 (± 0.94)	4.83 (± 0.85)	5.40 (± 0.85)	5.72 (± 0.48)	4.49 (± 0.94)
LFI D7	4.53 (± 1.01)	4.53 (± 1.01)	4.84 (± 0.77)	5.37 (± 0.87)	6.32 (± 0.4)	4.36 (± 0.92)
28-day mortality	13.75 %	37.66%	23.91%	47.92%	92.86%	9.44%
90-day mortality	24.26 %	55.19%	50%	60.42%	92.86%	18.64%
1-year mortality	39.98 %	59.09%	60.87%	72.92%	92.86%	35.21%

ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALD, alcohol liver disease; HAV, hepatitis A; HCB, hepatitis B; HCV, hepatitis C; LFI, Liver Frailty Index; MELD, Model of End-Stage Liver Disease Score; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

patients experiencing acute decompensation of ACLD, the ACLF status was evaluated using an online calculator provided by the EF-CLIF consortium.

ACLF status was evaluated using an online calculator provided by the EF-CLIF consortium. Detailed baseline characteristics are presented in table 1.

Liver Frailty Index

During hospitalisation, all patients underwent physical frailty testing using the LFI. LFI stands out in our liver and transplant registries as a diagnostic tool from the recommended array. The LFI assessment was performed by an experienced examiner at the beginning of hospitalisation and after 7 days. The examiner was blinded to the patient's ACLF grade. Both the initial and follow-up assessments were conducted by the same person. The prognostic significance of the LFI is evidenced by its association with a range of outcomes, including reduced quality of life, depression, extended hospital stays, higher likelihood of being removed from the LT waiting list, infections, increased mortality rates before and after LT and higher costs, among others.[40–43]

The LFI consists of three functional tests of physical performance, namely: (a) grip strength, the average of three measurements, while the patient's dominant limb is tested; (b) chair stand test, the time required for the patient to stand up and sit down five times from chairs; and (c) balance test, the part that the patient can stay in three positions (feet placed side to side, semitandem and tandem) is measured, while the maximum time is 10 s.[35 42]

LFI was calculated using a calculator available at http://liverfrailtyindex.ucsf.edu. LFI was measured in two time periods at patient admission and after 7 days of hospitalisation using:

(- 0.330 × gender-adjusted grip strength) + (- 2.529 × number of chair stands per second) + (- 0.040 × balance time) + 6

Patients were classified into three groups based on their LFI scores: robust, if their index is below 3.2, prefrail, if it falls between 3.2 and 4.5 and frail if it exceeds 4.5. The Delta D7 LFI, representing the change in LFI between two time points, was calculated as follows: Delta D7 LFI=LFI at day 1 minus LFI at day 7. An improvement in frailty status was indicated by a Delta D7 LFI >+0.1, while a decline in frailty was defined by a Delta D7 LFI <−0.1. Delta D7 LFI results ranging between −0.1 and +0.1 were classified as 'no change'.

The Model of ESLD Score

The current LT allocation system is based on the MELD score. The MELD score is a validated metric that predicts survival on the waiting list. The MELD score consists of serum bilirubin, creatinine, international normalised ratio, sodium and albumin. The MELD score is commonly used in liver transplant allocation systems to prioritise patients on the waiting list based on the severity of their liver disease. Higher MELD scores indicate a greater risk of mortality without a transplant and are associated with higher priority for receiving a donor liver.[44]

Acute chronic liver failure

ACLF is a clinical syndrome characterised by the sudden deterioration of liver function in individuals who already have chronic liver disease. ACLF typically involves the development of severe complications and organ failure, often requiring intensive medical attention. This condition is associated with a high mortality rate and represents a critical stage in the progression of liver disease. Patients with ACLF may experience symptoms such as jaundice, hepatic encephalopathy, coagulopathy and circulatory dysfunction.[45–47] The grading of ACLF is based on the liver-adjusted SOFA system, which is nowadays fully automated and available as a calculator on the internet (http://www.ef-clif.com). Roughly, ACLF grade 1 represents one failing organ/system, while ACLF 3 represents three or more; an upgrade of subclassification of ACLF is underway. The 90-day mortality rates for ACLF 1, 2 and 3 are 40.7%, 52.3% and 79.1%, respectively.[12]

Grade 1 (ACLF-1)

This describes the initial phase of ACLF characterised by a comparatively milder degree of severity. Individuals at this stage may experience one or more organ failures, yet the impairment is not as pronounced.

Grade 2 (ACLF-2)

This stage reflects a moderate level of ACLF severity. Patients in this category experience more pronounced organ failures, and the dysfunction is more significant compared with ACLF-1.

Grade 3 (ACLF-3)

This represents the utmost critical phase of ACLF, denoting a severe condition characterised by multiple and frequently profound organ failures. Patients with ACLF-3 face an elevated risk of mortality.

Statistical analysis

The data analysis was conducted using SPSS V.23.0 software, while initial characteristics were meticulously recorded in MS Excel 2016. To explore the collected data further, descriptive statistics were performed with SPSS. Moreover, regression analysis was applied to uncover relationships within the data. The Shapiro-Wilk test was used for assessing data normality. Based on the results of this normality test, both the nonparametric Mann-Whitney U test and the T-test were employed to evaluate the significance of differences between patients with liver cirrhosis. Kaplan-Meier survival analysis was conducted, and group differences were evaluated using the log-rank test. Statistical significance was established at the α =0.05 significance level.

Table 2 Liver Frailty Index assessment on first day

			LFI index	P value
LFI day 1	Mean		4.74 (±1.01)	
	Women		5.09 (± 0.92)	0.001
	Men		4.55 (±1.02	
	Up to 65 years		4.58 (±0.98)	0.0002
	Over 65 years		5.26 (±0.97)	
	Aetiology	ALD	4.80 (±0–96)	–0.168
		Others	4.52 (±1.20)	
	ACLD		4.51 (± 1.06)	
	ACLF	1	4.83 (± 0.85)	1 vs 2 –0.032
		2	5.40 (± 0.85)	2 vs 3 –0.346
		3	5.72 (± 0.48)	1 vs 3 –0.006
Number of patients in categories		Frail	192	–
		Prefrail	159	–
		Robust	45	–
Mortality		28 days	20.2 %	–
		90 days	33.84 %	–
		1 year	47.98 %	–

ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure; ALD, alcohol liver disease; LFI, Liver Frailty Index.

RESULTS

The entire analysed registry includes 1023 patients. Among the 1023 patients enrolled in RH7, 154 (15.1%) met the EASL-CLIF criteria for ACLF. The predominant cause of the underlying ACLD was ALD, accounting for 79.8% of cases. Out of the total number of patients with ACLF, 120 patients experienced mortality, representing a mortality rate of 77.9% in the entire group without any further specific subdivisions for acute liver failure. Among the total ACLF patients, LT was performed in 5 patients, accounting for 3.25%. Out of the 5 patients who underwent transplantation, 3 cases resulted in mortality. In the group of patients with ACLF=1, the mortality rate was recorded at 71.74%. For patients with ACLF=2, the mortality rate stands at 85.42%. The group of patients with ACLF=3 shows a mortality rate of 92.86%.

Table 2 provides a comprehensive analysis of the LFI measured on day 1 for patients with ACLD and ACLF. The LFI was 5.09 (± 0.92) in women and 4.55 (±1.02) in men. Additionally, the table shows mortality rates at 28 days, 90 days and 1 year.

Tables 3 and 4 present the changes in the LFI on day 7 after initial assessment among patients with ACLD and ACLF. The data are categorised into three outcomes:

Table 3 Delta LFI D7

		Improved	Stable	Worsened
LFI D7 (%)	Mean	28.54	59.60	11.86
	ACLD	27.63	63.81	8.56
	ACLF	30.22	51.80	17.98
	ACLF in categories			
	1	28.99	50.72	20.29
	2	26.83	56.10	17.07
	3	37.93	48.28	13.79
P value (LFI D7)	ACLD vs ACLF	0.030	0.156	0.136
	ACLF=1 vs ACLF=2	0.009	0.358	0.319
	ACLF=1 vs ACLF=3	0.640	0.07	0.028
	ACLF=2 vs ACLF=3	0.427	0.022	0.141

ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure; LFI, Liver Frailty Index.

Table 4 Delta LFI according to ACLF and ACLD

	ACLD (n=242)	ACLF 1 (n=92)	ACLF 2 (n=48)	ACLF 3 (n=14)	P value
LFI baseline	4.51 (± 1.06)	4.83 (± 0.85)	5.40 (± 0.85)	5.72 (± 0.48)	0.0002
LFI day 7	4.41 (± 1.17)	4.84 (± 0.77)	5.37 (± 0.87)	6.32 (± 0.39)	0.0042
Delta D7 LFI	−1.05 (± 1.28)	+0.51 (± 1.12)	−1.51 (± 0.24)	+1.15 (± 0.31)	0.0119

ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure; LFI, Liver Frailty Index.

improved, stable and worsened. On day 7, 28.54% of patients showed improvement in their LFI score, 59.60% remained stable and 11.86% worsened. Statistical comparison between ACLD and ACLF showed a significant difference in improvement rates (p=0.030), but no significant difference in stability (p=0.156) or worsening rates (p=0.136). When comparing ACLF categories, significant differences were found between ACLF=1 and ACLF=2 (p=0.009) in improvement rates, indicating variability in response among ACLF patients. The comparison of stability between ACLF=1 and ACLF=3 showed a nearly significant trend (p=0.07) and a significant difference in worsening rates (p=0.028), highlighting the impact of different ACLF categories on patient outcomes. No significant differences were found between ACLF=2 and ACLF=3 in improvement or worsening, but a significant difference was noted in stability (p=0.022).

The number of patients at risk at specific time points for each group (ACLD, ACLF 1, ACLF 2 and ACLF 3) was analysed. For patients with ACLD, the numbers at risk were as follows: 242 at baseline, 119 at 1000 days, 98 at 2000 days, 95 at 3000 days and 95 at 4000 days. For ACLF 1, the corresponding numbers were 92, 29, 27, 26 and 26, respectively. Patients with ACLF 2 had 48 at baseline, 10 at 1000 days, 8 at 2000 days, 7 at 3000 days and 7 at 4000 days. For ACLF 3, the numbers at risk were 14 at baseline, 1 at 1000 days and 1 at each subsequent time point (2000, 3000 and 4000 days) (figure 1).

The number of subjects at risk for ACLD and ACLF stages 1, 2 and 3 was evaluated at time points 0 days, 7 days, 14 days, 21 days and 28 days. For ACLD, the number at risk decreased from 22 at baseline to 17, 10, 4 and 0 by day 28. In ACLF stage 1, the number at risk declined from 22 at baseline to 16, 9, 5 and 1. For ACLF stage 2, the number at risk progressively reduced from 23 at baseline to 18, 11, 7 and 2. In ACLF stage 3, the number at risk showed a more rapid decline from 13 at baseline to 5, 3, 1 and 0. These findings demonstrate a progressive decrease in the number of subjects at risk over time, with a steeper decline observed in ACLF stage 3, indicating poorer survival outcomes in more advanced stages of disease (figure 2).

Kaplan-Meier survival curves stratified by LFI over the first 7 days of hospitalisation are presented in figure 1. Among patients with ACLD, survival probability was significantly higher in the group with improved LFI compared with those with stable or worsened LFI (p=0.013 for improved vs stable; p=0.031 for stable vs worsened), indicating a meaningful association between early improvement in frailty and long-term survival. In contrast, the survival curves for patients with ACLF grade 1 displayed no statistically significant differences were observed between the LFI dynamic groups (all p>0.05). For ACLF grade 2, survival probability was uniformly low across all groups, and the Kaplan-Meier curves again showed no significant divergence, indicating a limited prognostic impact of LFI dynamics at this stage. Patients with ACLF grade 3 exhibited markedly poor survival regardless of LFI improvement, with all curves approaching zero within a short follow-up period.

28-day Kaplan-Meier survival analysis stratified by changes in LFI is illustrated in figure 2. In patients with ACLD, survival curves for the improved, stable and worsened LFI groups did not show statistically significant differences (p=0.977 for improved vs stable; p=0.766 for improved vs worsened; p=0.075 for stable vs worsened). Among patients with ACLF grade 1, there was a separation of survival curves favouring improved and worsened groups over the stable group; however, none of the comparisons reached statistical significance (all p>0.05). In the ACLF grade 2 subgroup, the 28-day survival curves again did not demonstrate statistically significant differences, although a slight advantage was observed in the worsened group (possibly due to early mortality censoring or group imbalance), with p values ranging from 0.062 to 0.429.

In the ACLF grade 3 subgroup, early mortality was universally high across all LFI categories. While no statistically significant differences were detected (p=0.98–0.041).

DISCUSSION

In this study, we sought to explore whether serial monitoring of LFI during hospitalisation offers additional prognostic value over a single assessment at admission. The underlying hypothesis was that improvement in frailty status—reflected by an LFI score over time—could be associated with better clinical outcomes, including reduced mortality. This concept was grounded in the idea that frailty is a dynamic condition and that changes during hospitalisation may reflect a patient's physiological resilience and response to treatment. However, our results did not support this hypothesis. While LFI measured on day 7 did correlate with mortality, it did not significantly outperform the predictive value of LFI at admission. These findings suggest that early frailty assessment

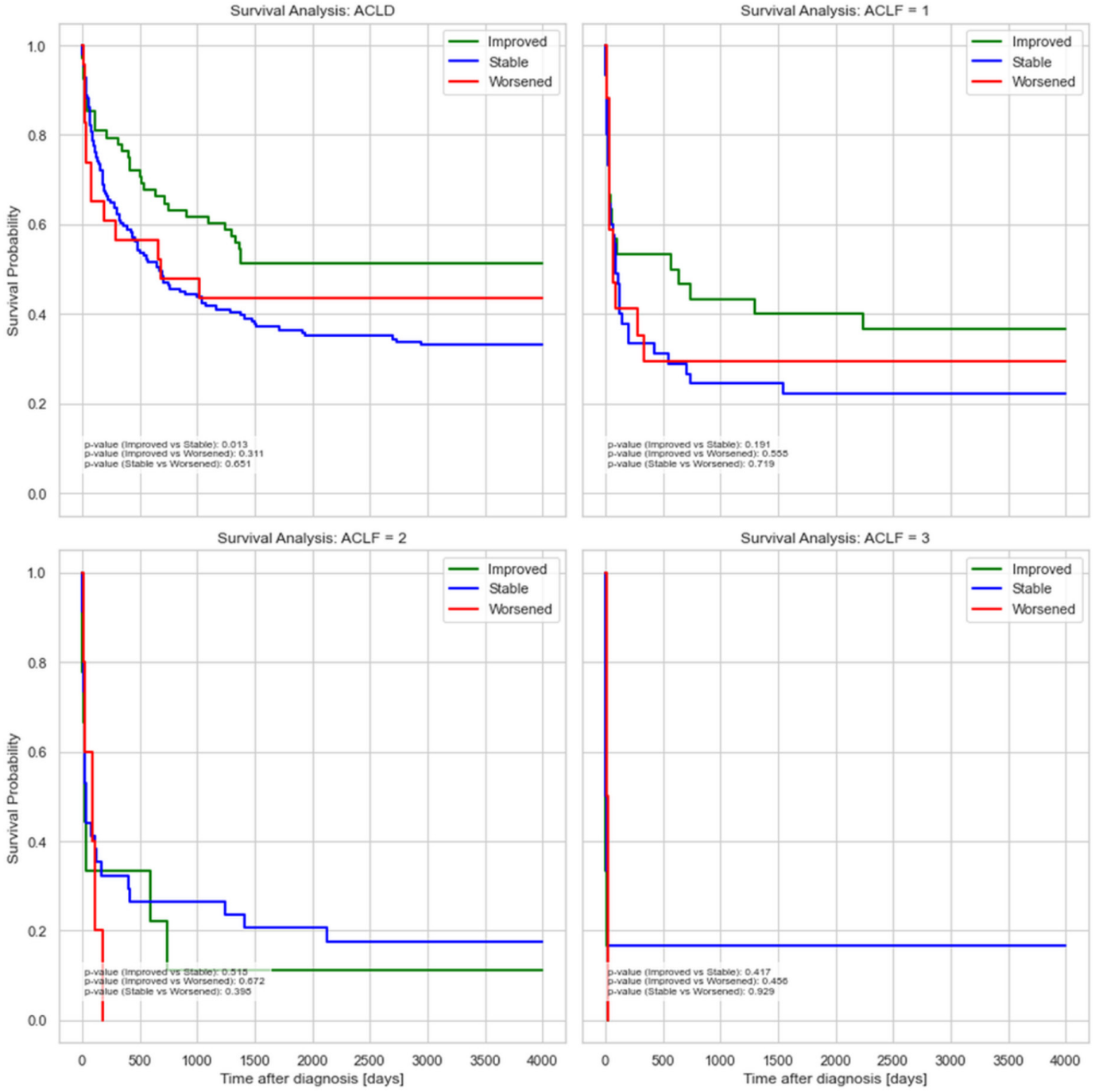

Figure 1 Survival probability. ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure.

remains a strong prognostic tool and that changes in LFI during a short hospitalisation period may not meaningfully alter risk stratification.

LFI provided us with prognostic information above and beyond the liver-specific prognostic systems such as MELD.[48] We were motivated to assess the dynamics of LFI not only because of the high prevalence and short-term mortality associated with ACLF, but also because of its brevity, availability and validity.[49] Liver-specific prognostic systems do not capture the overall capacity of the organism to withstand novel stressors such as LT. Although the incorporation of point-of-care LFI measurement improved our ability to predict outcomes in ACLF, there was still significant room for improvement, as evidenced by the mortality rate of our ACLF 3 patients after LT. Our results showed that LFI measured on day 7 post-admission had a significant impact on predicting the survival of patients with ACLF, but its additional predictive value over the LFI measured at admission (day 1) is not substantial.

ACLD is characterised by a long asymptomatic period, which can last for many years. If it is not detected by screening or by chance, it typically becomes apparent through decompensating events such as jaundice, bleeding or even liver cancer. At this stage, the biological

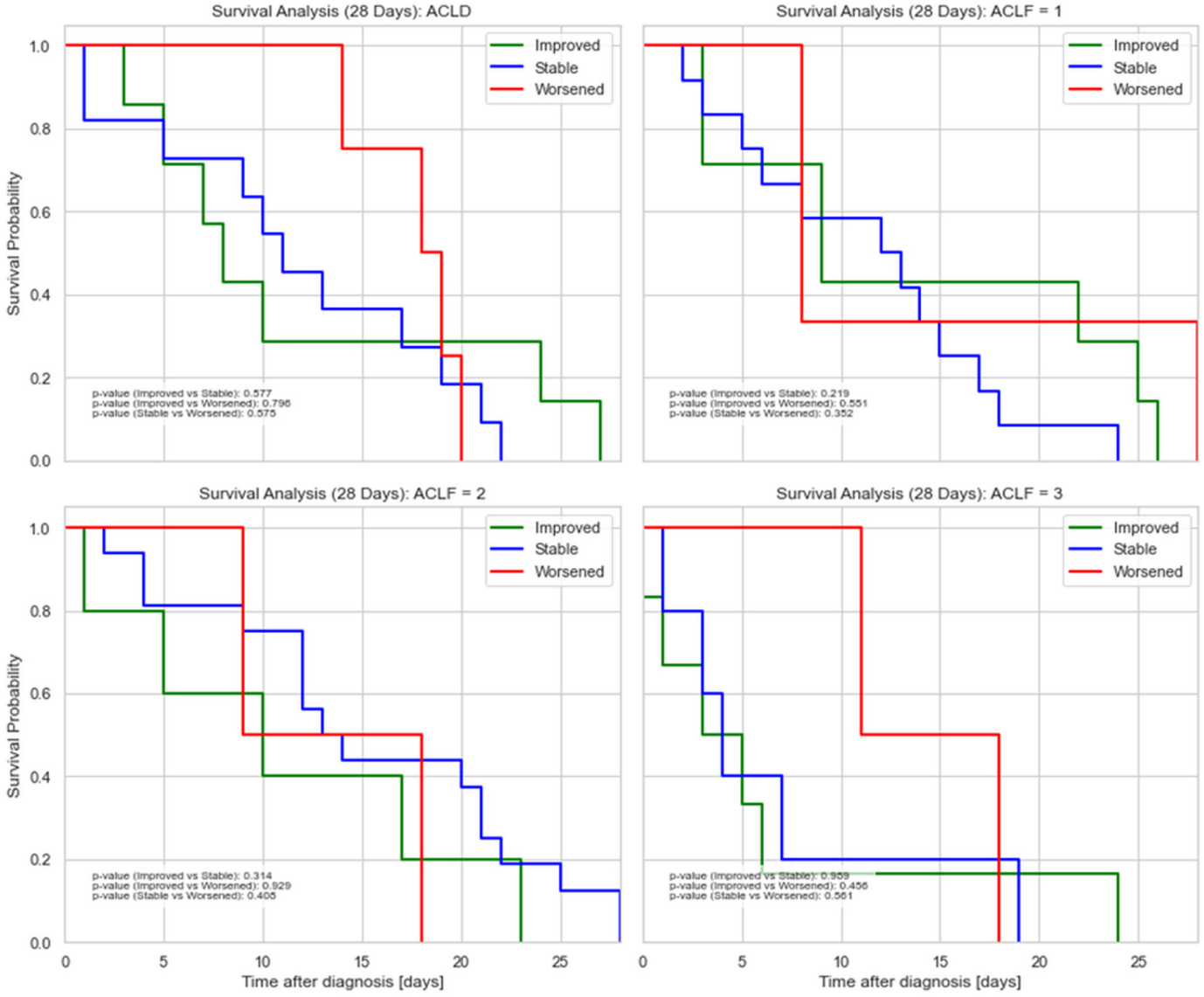

Figure 2 Survival analysis (28 days). ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure.

reserves of the organism might be exhausted to various degrees; that is, the syndrome of frailty may or may not be present.[50] Patients with ACLD are susceptible to frailty due to a multitude of reasons associated with the vital metabolic and immunologic functions of the liver. Thorough consideration of the overall health of the patient—including comorbidities, nutritional status, sarcopenia and physical and cognitive performance—can help caregivers to better understand prognosis, especially vis-a-vis challenges such as LT. In this line, a comprehensive approach to patient care, including nutritional intervention and prehabilitation, can significantly impact the overall course of the disease.[49]

The association between baseline frailty and the progression of liver cirrhosis was tested in a study by Wang *et al*.[39] A total of 822 patients from North America and one from India were included. In patients with compensated cirrhosis, being frail versus robust was associated with an increased risk of progression to the next cirrhosis stage or death (HR, 2.45; 95% CI, 1.14 to 5.29) and an increased risk of unplanned hospitalisations (2.32; 95% CI, 1.13 to 4.79). Lai *et al*[35] have analysed 1093 outpatients with liver cirrhosis. Patients with severe frailty impairment had a worse baseline LFI score and a higher likelihood of having NAFLD, diabetes or dependence on dialysis. The competing risk regression of death/removal from the LT waiting list increased with the worsening of the LFI. In the competing risk regression adjusted for baseline LFI, age, height, MELD and albumin, a change in LFI by 0.1 units over 3 months was associated with a 2.04-fold increased risk of death/removal (95% CI, 1.35 to 3.09). Guo *et al*[51] assess the impact of sarcopenia and frailty on the survival of a group of hospitalised individuals with cirrhosis. The prevalence of frailty was notably greater in the cohort of patients with sarcopenia compared with those without sarcopenia (27.1% vs 11%, p=0.009). In the survival analysis, the sarcopenic-frail group demonstrated an elevated hazard ratio (2.604 in model 1; 4.294 in model 2) for mortality when contrasted with the non-sarcopenic non-frail group.

Our results should be interpreted in the context of the documented importance of the dynamics of frailty. Improvement in frailty by the appropriate intervention (nutrition, rehabilitation) can be associated with an improved prognosis.[52]

This study has several limitations that should be considered when interpreting the findings. First, the single-centre design may limit the generalisability of the results to other populations and healthcare systems. Differences in patient management, healthcare infrastructure and rehabilitation strategies could influence the external validity of our conclusions. Observational window—limited to changes over the first 7 days of hospitalisation—may not be sufficient to detect clinically meaningful improvements or deteriorations in frailty status. Frailty is a dynamic condition, but it may require a longer timeframe to observe significant change, especially in patients with ACLF. The low number of patients undergoing liver transplantation in the ACLF subgroup reduces the ability to explore how changes in LFI may interact with post-transplant outcomes. Future multicentre studies with larger and more diverse cohorts, longer follow-up periods and broader frailty assessments are warranted to validate and expand on these findings.

CONCLUSION

The impact of day 7 LFI on the survival of individuals battling ACLF is significant within the medical field. Despite this significance, day 7 LFI does not offer a substantial improvement in outcome prediction compared with the initial LFI assessment at the time of admission. As a result, day 1 LFI continues to be the primary and widely recognised tool for promptly identifying patients with ACLF. This early recognition, enabled by day 1 LFI, is crucial in the continuum of patient care. Whether the objective is to initiate palliative care, apply established treatment protocols or urgently consider secondary interventions, such as plasmapheresis or immediate liver transplantation, by depending on the day 1 LFI, healthcare providers can adeptly manage the complexities of ACLF, aiming for the best possible patient care outcomes.

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Contributors ĽS and PK: conceptualisation. ĽS and PK: methodology. ĽS, DŽ and SAS: validation and supervision. KM: formal analysis. ĽS, KM, DH and KŠ: investigation. DL, ĽS and DŽ: writing. DL, ĽS, KM and DH: original draft preparation. ĽS, DL, KM, DH, SAS, KŠ and DŽ: writing—review and editing. SAS and ĽS: project administration. All authors contributed to the article and approved the submitted version. Guarantor: DL.

Funding Funded by the EU NextGenerationEU through the Recovery and Resilience Plan for Slovakia under the project No. 09I03-03-V05-00009".

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and the study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki. Ethical approval was given by the ethics committee of the Roosevelt Hospital in Banská Bystrica under number 15072. None of the patients were institutionalised. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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REFERENCES

1 Sepanlou SG, Safiri S, Bisignano C. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020;5:245–66.
2 Costa D, Simbrunner B, Jachs M, *et al*. Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality. *J Hepatol* 2021;74:819–28.
3 Zhou W-C, Zhang Q-B, Qiao L. Pathogenesis of liver cirrhosis. *World J Gastroenterol* 2014;20:7312–24.
4 Shearer JE, Jones R, Parker R, *et al*. The Natural History of Advanced Chronic Liver Disease Defined by Transient Elastography. *Clin Gastroenterol Hepatol* 2023;21:694–703.
5 Canillas L, Pelegrina A, Álvarez J, *et al*. Clinical Guideline on Perioperative Management of Patients with Advanced Chronic Liver Disease. *Life (Basel)* 2023;13:132.
6 Asrani SK, Devarbhavi H, Eaton J, *et al*. Burden of liver diseases in the world. *J Hepatol* 2019;70:151–71.
7 Moon D-B, Lee S-G. Liver transplantation. *Gut Liver* 2009;3:145–65.
8 Marroni CA, Fleck AM Jr, Fernandes SA, *et al*. Liver transplantation and alcoholic liver disease: History, controversies, and considerations. *World J Gastroenterol* 2018;24:2785–805.
9 Fernández-Alonso V, Hernández-Matías AM, Díaz-Serrano MT, *et al*. Analysis of the impact of liver transplantation as a condition of health. *Enferm Clin (Engl Ed)* 2022;32:249–56.
10 Skladaný Ľ, Adamcová Selčanová S, Janičko M, *et al*. Acute decompensation (AD) of advanced chronic liver disease (ACLD) and hepatitis E virus (HEV) infection as the trigger. *Klin Mikrobiol Infekc Lek* 2018;24:82–7.
11 Simbrunner B, Caparrós E, Neuwirth T, *et al*. Bacterial translocation occurs early in cirrhosis and triggers a selective inflammatory response. *Hepatol Int* 2023;17:1045–56.
12 Moreau R, Jalan R, Gines P, *et al*. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–37.
13 Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56.
14 Kamath PS, Kim WR, Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology* 2007;45:797–805.
15 Roth JA, Chrobak C, Schädelin S, *et al*. MELD score as a predictor of mortality, length of hospital stay, and disease burden: A single-center retrospective study in 39,323 inpatients. *Medicine (Baltimore)* 2017;96:e7155.
16 Tsoris A, Marlar CA. Use of the child pugh score in liver disease. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2022.
17 Moreno R, Rhodes A, Piquilloud L, *et al*. The Sequential Organ Failure Assessment (SOFA) Score: has the time come for an update? *Crit Care* 2023;27:15.
18 Haj Ali S, Abu Sneineh A, Hasweh R. Nutritional assessment in patients with liver cirrhosis. *World J Hepatol* 2022;14:1694–703.

19 Jehan FS, Pandit V, Khreiss M, *et al*. Frailty Predicts Loss of Independence After Liver Surgery. *J Gastrointest Surg* 2022;26:2496–502.
20 Laube R, Wang H, Park L, *et al*. Frailty in advanced liver disease. *Liver Int* 2018;38:2117–28.
21 Naimimohasses S, O'Gorman P, McCormick E, *et al*. Prevalence of frailty in patients with non-cirrhotic non-alcoholic fatty liver disease. *BMJ Open Gastroenterol* 2022;9:e000861.
22 Kremer WM, Nagel M, Reuter M, *et al*. Validation of the Clinical Frailty Scale for the Prediction of Mortality in Patients With Liver Cirrhosis. *Clin Transl Gastroenterol* 2020;11:e00211.
23 Saraswat VA, Kumar K. Untangling the Web of Malnutrition, Sarcopenia, and Frailty in Chronic Liver Disease. *J Clin Exp Hepatol* 2022;12:268–71.
24 Zuberi BF, Rasheed T, Ali FS, *et al*. Assessment of frailty in cirrhosis using bedside measures and its correlation with Child-Turcotte-Pugh, MELD & MELD-Na Scores. *Pak J Med Sci* 2022;38:1086–92.
25 Lang P-O, Michel J-P, Zekry D. Frailty syndrome: a transitional state in a dynamic process. *Gerontology* 2009;55:539–49.
26 Roh E, Hwang SY, Yoo HJ, *et al*. Impact of non-alcoholic fatty liver disease on the risk of sarcopenia: a nationwide multicenter prospective study. *Hepatol Int* 2022;16:545–54.
27 Siyu L, Yuan Y, Ran A, *et al*. Frailty as tested by the Liver Frailty Index in out-patient patients with cirrhosis in China: a cross-sectional study. *Eur J Gastroenterol Hepatol* 2023;35:440–4.
28 Klein CG, Malamutmann E, Latuske J, *et al*. Frailty as a predictive factor for survival after liver transplantation, especially for patients with MELD≤15-a prospective study. *Langenbecks Arch Surg* 2021;406:1963–9.
29 Lai JC, Shui AM, Duarte-Rojo A, *et al*. Frailty, mortality, and health care utilization after liver transplantation: From the Multicenter Functional Assessment in Liver Transplantation (FrAILT) Study. *Hepatology* 2022;75:1471–9.
30 Lin F-P, Visina JM, Bloomer PM, *et al*. Prehabilitation-Driven Changes in Frailty Metrics Predict Mortality in Patients With Advanced Liver Disease. *Am J Gastroenterol* 2021;116:2105–17.
31 Singh S, Taneja S, Tandon P, *et al*. A Comparison of Different Frailty Scores and Impact of Frailty on Outcome in Patients With Cirrhosis. *J Clin Exp Hepatol* 2022;12:398–408.
32 Soto R, Díaz LA, Rivas V, *et al*. Frailty and reduced gait speed are independently related to mortality of cirrhotic patients in long-term follow-up. *Ann Hepatol* 2021;25:100327.
33 Lanthier N, Stärkel P, Dahlqvist G. Frailty, sarcopenia and mortality in cirrhosis: what is the best assessment, how to interpret the data correctly and what interventions are possible? *Clin Res Hepatol Gastroenterol* 2021;45:101661.
34 Kao J, Reid N, Hubbard RE, *et al*. Frailty and solid-organ transplant candidates: a scoping review. *BMC Geriatr* 2022;22:864.
35 Lai JC, Dodge JL, Kappus MR, *et al*. Changes in frailty are associated with waitlist mortality in patients with cirrhosis. *J Hepatol* 2020;73:575–81.
36 Ha NB, Fan B, Shui AM, *et al*. CT-quantified sarcopenic visceral obesity is associated with poor transplant waitlist mortality in patients with cirrhosis. *Liver Transpl* 2023;29:476–84.
37 Iacob S, Mina V, Mandea M, *et al*. Assessment of Sarcopenia Related Quality of Life Using SarQoL® Questionnaire in Patients With Liver Cirrhosis. *Front Nutr* 2022;9:774044.
38 Englesbe MJ, Patel SP, He K, *et al*. Sarcopenia and Post-Liver Transplant Mortality. *J Am Coll Surg* 2010;211:271–8.
39 Wang S, Whitlock R, Xu C, *et al*. Frailty is associated with increased risk of cirrhosis disease progression and death. *Hepatology* 2022;75:600–9.
40 Lai JC, Covinsky KE, Dodge JL, *et al*. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017;66:564–74.
41 Lai JC, Covinsky KE, McCulloch CE, *et al*. The Liver Frailty Index Improves Mortality Prediction of the Subjective Clinician Assessment in Patients With Cirrhosis. *Am J Gastroenterol* 2018;113:235–42.
42 Wang CW, Lebsack A, Chau S, *et al*. The Range and Reproducibility of the Liver Frailty Index. *Liver Transpl* 2019;25:841–7.
43 Wang M, Shui AM, Ruck J, *et al*. Clinically relevant cut-points for changes in the Liver Frailty Index are associated with waitlist mortality in patients with cirrhosis. *Liver Transpl* 2024;30:991–1001.
44 Ge J, Kim WR, Lai JC, *et al*. "Beyond MELD" - Emerging strategies and technologies for improving mortality prediction, organ allocation and outcomes in liver transplantation. *J Hepatol* 2022;76:1318–29.
45 Hernaez R, Solà E, Moreau R, *et al*. Acute-on-chronic liver failure: an update. *Gut* 2017;66:541–53.
46 Kumar R, Mehta G, Jalan R. Acute-on-chronic liver failure. *Clin Med (Lond)* 2020;20:501–4.
47 Shah NJ, Mousa OY, Syed K, *et al*. Acute on chronic liver failure. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2023.
48 Skladany L, Molcan P, Vnencakova J, *et al*. Frailty in Nonalcoholic Fatty Liver Cirrhosis: A Comparison with Alcoholic Cirrhosis, Risk Patterns, and Impact on Prognosis. *Can J Gastroenterol Hepatol* 2021;2021:5576531.
49 Lai JC, Tandon P, Bernal W, *et al*. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021;74:1611–44.
50 Skladany L, Drotarova Z, Vnencakova J, *et al*. Applicability and prognostic value of frailty assessment tools among hospitalized patients with advanced chronic liver disease. *Croat Med J* 2021;62:8–16.
51 Guo G, Li C, Hui Y, *et al*. Sarcopenia and frailty combined increases the risk of mortality in patients with decompensated cirrhosis. *Ther Adv Chronic Dis* 2022;13:20406223221109651.
52 Trivedi HD, Tapper EB. Interventions to improve physical function and prevent adverse events in cirrhosis. *Gastroenterol Rep (Oxf)* 2018;6:13–20.