# Validation of the Clinical Frailty Scale for the Prediction of Mortality in Patients With Liver Cirrhosis

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INTRODUCTION: **Frailty is a common but often underestimated complication in patients with liver cirrhosis. The Clinical Frailty Scale (CFS) allows the assessment of frailty within a short period of time but has only been investigated in a Canadian cohort of outpatients. The aim of the current study was to evaluate the ability of the CFS to predict mortality in outpatients and nonelectively hospitalized German patients.**

METHODS: **Two hundred outpatients and 99 nonelectively hospitalized patients with liver cirrhosis were prospectively enrolled. Outpatients/inpatients were followed for a median of 364/28 days regarding the primary outcome of death or liver transplantation. Eighty-seven patients of the outpatient cohort and 64 patients of the inpatient cohort had available computed tomography-scans for the quantification of muscle mass.**

RESULTS: **Median CFS was 3 in the outpatient and the inpatient cohort. Twenty-one (10.5%) outpatients were at least prefrail (CFS > 3) and 26 (26.3%) inpatients were frail (CFS > 4). For every one-unit increase, there was an independent association between the CFS and mortality in the outpatient cohort (hazard ratio 1.534, $P = 0.007$). This association remained significant after controlling for muscle mass in the subcohort with available computed tomography scans. In the inpatient cohort, frailty (CFS > 4) was an independent predictor for 28-day mortality after controlling for acute-on-chronic liver failure, albumin, and infections (odds ratio 4.627, $P = 0.045$). However, this association did not reach significance in a subcohort after controlling for muscle mass.**

DISCUSSION: **Especially in outpatients, CFS is a useful predictor regarding increased mortality independent of the muscle mass.**

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/CTG/A310

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## INTRODUCTION

Liver cirrhosis is a common cause for morbidity and mortality contributing to over 1 million deaths in 2010 (1). Prognostication in patients with liver cirrhosis is routinely performed by using traditional tools such as the Child-Pugh (CP) score or the model for end-stage liver disease (MELD) (2,3). However, these scores do not consider the patient in a holistic way but rather focus on liver function or the presence of complications of liver cirrhosis. In recent years, many studies demonstrated that sarcopenia is an important prognostic factor independent of CP or MELD (4,5). First measurement techniques included the bioelectrical impedance analysis and dual x-ray absorptiometry but recent radiological descriptions of abdominal muscle indices seem to be more reliable. The skeletal muscle index assessed by the cross-sectional area of several muscles on computed tomography (CT) at the L3 vertebral level is nowadays the most widely used technique. Recent studies have indicated that more easily and faster measurable indices such as the transversal psoas muscle area (TPMA) have an equivalent predictive value such as the more complex skeletal muscle index (4). However, some factors, e.g., ascites and muscle edema, may influence measurements. In addition, these techniques do not measure the overall functional reserve of the respective patient. This loss of functional reserve is called frailty (6)—a syndrome of decreased reserve and resistance to stressors and a multifactorial construct of a cumulative decline in different physiological systems (7). There is some evidence that frailty is associated with poorer prognosis not only in patients with liver cirrhosis but also in many other end-stage diseases and may also negatively affect the health-

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related quality of life (8–11). Recently, the Clinical Frailty Scale (CFS) was introduced as a promising, easy-to-handle, and inexpensive tool to assess and score frailty in clinical practice (12). Patients are assessed according to 9 categories ranging from very fit to severely frail. A Canadian study by Tandon et al. (9) demonstrated that the CFS is comparable with more time-consuming frailty tests such as the Fried Frailty Criteria or the Short Physical Performance Battery to predict mortality and hospitalization in patients with liver cirrhosis. However, the ability of CFS has only been investigated in a North-American cohort of outpatients without consideration of the amount of muscle mass. Frailty and sarcopenia may be causally linked and used as surrogates; however, doubts recently arose about a close correlation. Therefore, it was the aim of the current study (i) to evaluate the ability of the CFS to predict mortality in outpatients and nonelectively hospitalized German patients with liver cirrhosis and (ii) to investigate the predictive properties of CFS under consideration of the muscle mass of the respective patients.

## METHODS

### Patients

Data of 2 prospectively recruited cohorts of patients with liver cirrhosis were analyzed.

***Cohort 1 (outpatient cohort).*** Two hundred eighteen patients with liver cirrhosis were prospectively enrolled into the study between March 2017 and December 2018 at the Cirrhosis Center Mainz of the University Medical Center of the Johannes Gutenberg-University in Mainz, Germany. Data were mainly collected for an ongoing database that aimed to investigate the impact of covert hepatic encephalopathy (CHE) on health-related quality of life and to develop the clinical CHE score, which was described elsewhere (13,14). Detailed inclusion and exclusion criteria and recruitment procedures are also described elsewhere (13,14). All patients were either outpatients or electively hospitalized for preplanned procedures. Reasons for hospitalization were mainly to perform liver biopsy, endoscopic therapy of varices, preplanned ascites puncture or evaluation for liver transplantation. The leading etiology of the underlying liver disease was determined according to clinical, serological and histological findings. Diagnosis of liver cirrhosis was established by histology, conclusive appearance in ultrasound or radiological imaging, endoscopic features of portal hypertension and medical history. Blood biochemistry (bilirubin, albumin, international normalized ratio, sodium, potassium, creatinine, c-reactive protein, white blood cell count, hemoglobin, and thrombocytes) were assessed in all patients. MELD and CP scores were calculated to determine the severity of underlying liver disease. Patients were excluded if they fulfilled one or more of the following criteria: previous episode of overt hepatic encephalopathy (OHE) during the past 6 weeks, chronic alcohol consumption during the past 3 months, any intake of psychotropic drugs or opioids, the presence of severe comorbidities (heart disease New York Heart Association III–IV, chronic obstructive pulmonary disease Gold C and D, and renal failure with creatinine $>$ 1.5 mg/dL), the presence of hepatocellular carcinoma (HCC) or other active malignancies, history of transjugular intrahepatic portosystemic shunt, neurological comorbidities (i.e., dementia or history of stroke), history of recent head trauma and electrolyte disorders (serum potassium $<$3.5 mg/dL or $>$5 mg/dL and serum sodium $<$130 mg/dL or $>$150 mg/dL). Patients with a previous episode of OHE more than 6 weeks ago were allowed to participate if they were on consequent therapy with lactulose and/or rifaximin, if clinically indicated.

***Cohort 2 (nonelectively hospitalized patient cohort).*** Ninety-nine consecutive inpatients were prospectively enrolled into the study between March 2019 and October 2019 at the Cirrhosis Center Mainz of the University Medical Center of the Johannes Gutenberg-University in Mainz, Germany. All patients were nonelectively hospitalized most often because of complications of liver cirrhosis, acute-on-chronic liver failure (ACLF) or infections and initially treated on normal wards. All data were recorded within the first 24 hours of hospitalization. The leading etiology of underlying liver disease and diagnosis of liver cirrhosis were established as described above. Blood biochemistry (described above) was assessed in all patients at the day of study inclusion. Every patient was closely monitored for development of ACLF or infections during hospital stay. ACLF was defined according to the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) recommendations (15,16). Patients with malignancies (e.g., HCC) or unwillingness to stop alcohol abuse were not considered for this study.

### Diagnosis of hepatic encephalopathy

Patients recruited for the outpatient cohort were evaluated for the presence of CHE using the West Haven criteria and the portosystemic encephalopathy syndrome test. The detailed procedures are described elsewhere (14,17). Patients recruited for the inpatient cohort were evaluated for the presence of OHE using the West Haven criteria.

### Assessment of frailty

The CFS, which has been evaluated recently in patients with liver cirrhosis and described in detail elsewhere, was used to assess frailty (9,12). The CFS is based on clinical assessment and divided into 9 categories according to patients daily functioning (1: very fit, 2: well, 3: well with treated comorbid diseases, 4: apparently vulnerable, 5: mildly frail, 6: moderately frail, 7: severely frail, 8: very severely frail, and 9: terminally ill). According to accepted definitions, frailty was defined as a CFS $>$ 4 (CFS 5–9) and prefrailty as a CFS $>$ 3 (CFS 4–9).

### Assessment of muscle mass

To assess muscle mass, we determined the TPMA (4,5). According to recent studies, one axial image at the level of L3/L4 vertebral body was taken for the measurement of TPMA. Both psoas areas in $mm^2$ were added, divided by 2, and adjusted to the patient's squared height. The patient's height was taken on the day of inclusion. Because accepted cutoffs for low muscle mass are still lacking, we divided both cohorts according to the respective TPMA medians for men and women into groups with low muscle mass (TPMA below the respective median) and high muscle mass (TPMA above the respective median).

CT scans were analyzed retrospectively, and only scans within a three-month period prestudy or poststudy inclusion were evaluated.

### Follow-up evaluation

As described elsewhere (18), all patients of the outpatient cohort were followed up during study visits every 6 months in the

outpatient clinic. The primary endpoint evaluated during the follow-up was the composite of death or need for liver transplantation. Given that all patients who had received a liver transplantation had done so because of final hepatic failure, they were treated as complete cases (death). In patients with alcoholic liver cirrhosis, a minimum 6-month period of alcohol abstinence before liver transplantation was mandatory. Patients who did not show up to the follow-up examination were contacted by telephone to assess unplanned hospitalizations in other hospitals or death. In addition, the respective general practitioners were contacted in these cases.

All patients of the inpatient cohort were followed up during their hospital stay and for the following 28 days after study inclusion. The composite endpoint of death or liver transplantation was evaluated as the primary endpoint during the follow-up. Because patients with HCC were excluded, all patients who had received a liver transplantation had done so because of final hepatic failure and were consequently treated as complete cases (death).

## Ethics

The study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study protocols were approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (Nr. 837.232.17 [11066]) and Nr. 837.052.12 [8153]). Written informed consent was obtained from every participant.

## Statistical analysis

Quantitative data are expressed as medians with interquartile ranges (IQRs). Pairwise comparisons for quantitative variables were performed with an unpaired t-test or with the Mann-Whitney U test. Categorical variables are given as frequencies and percentages, respectively. For the comparison of 2 or more patient groups, a $\chi^2$ test was applied.

For the outpatient cohort, a survival curve for the CFS was analyzed using the Kaplan-Meier method and log-rank test. In addition, univariable Cox regression analyses were conducted for different variables. Variables with a $P$-value $< 0.05$ in univariable analyses were included into a multivariable Cox regression model with a stepwise variable selection procedure.

For the inpatient cohort, the differences between patients who deceased within 28 days or who survived were assessed by univariable analyses. Variables with $P < 0.05$ in the univariable analysis were subsequently considered in a multivariable logistic regression model. This regression model was first built based on a stepwise variable selection procedure. In addition, multiple logistic regression models were conducted with different variable combinations as described in Table 4.

All regression models were repeated for the subcohorts with available CT scans.

Our complete data analysis is exploratory. Hence, no adjustments for multiple testing were performed. For all tests, we used a 0.05 level to define statistically relevant deviations from the

**Table 1. Demographics and clinical characteristics of the entire outpatient cohort and stratified by (pre)frailty (CFS > 3) at the time of study inclusion**

| Variable | All patients | Not frail (CFS ≤ 3) | (Pre)Frail (CFS > 3) | *P* value |
|---|---|---|---|---|
| N | 200 | 179 | 21 | |
| Age, yr (IQR) | 60 (52–66) | 60 (52–65) | 57 (53–67) | 0.657 |
| Male gender, n (%) | 113 (56.5) | 101 (56.4) | 9 (42.9) | 0.950 |
| BMI (IQR) | 26.1 (23.2–31.7) | 26.1 (23.3–31.6) | 25.2 (22.4–32.5) | 0.689 |
| Etiology | | | | 0.071 |
| Alcohol, n (%) | 59 (29.5) | 49 (27.4) | 10 (47.6) | |
| Viral hepatitis, n (%) | 44 (22.0) | 43 (24.0) | 1 (4.8) | |
| NAFLD, n (%) | 26 (13.0) | 20 (11.2) | 6 (28.6) | |
| Other/mixed, n (%) | 71 (35.5) | 67 (37.4) | 4 (19.0) | |
| Median MELD score (IQR) | 10 (7–14) | 10 (7–13) | 14 (11–19) | 0.001 |
| CP A/B/C, n (%) | 120/63/17 | 115/50/14 | 5/13/3 | 0.002 |
| History of ascites, n (%) | 104 (52.0) | 88 (49.2) | 16 (76.2) | 0.019 |
| Ascites at study inclusion, n (%) | 44 (22.0) | 34 (19.0) | 10 (47.6) | 0.003 |
| History of OHE, n (%) | 29 (14.5) | 18 (10.1) | 11 (52.4) | <0.001 |
| Presence of CHE, n (%) | 64 (32.0) | 51 (28.5) | 13 (61.9) | 0.002 |
| Albumin, g/L (IQR) | 34 (29–38) | 35 (30–39) | 29 (25–34) | 0.001 |
| Sodium, mmol/L (IQR) | 139 (137–140) | 139 (137–140) | 138 (134–141) | 0.448 |
| CFS (as a metric variable) | 3 (2–3) | | | |
| Prefrailty (CFS > 3) | 21 (10.5) | | | |

Data are expressed as medians and IQRs or as frequencies and percentages.
BMI, body mass index; CFS, Clinical Frailty Scale; CHE, covert hepatic encephalopathy; CP, Child-Pugh; IQR, interquartile range; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; OHE, overt hepatic encephalopathy.

**Table 2. Analyses of potential predictors for the composite of death or need for liver transplantation (mortality) in cohort 1 using univariable and multivariable Cox regression models**

| | Univariable Cox regression analysis | | Multivariable Cox regression analysis | |
|---|---|---|---|---|
| | HR | *P* value | HR | *P* value |
| Age, yr | 0.991 (0.963–1.019) | 0.528 | | |
| Gender | 1.009 (0.532–1.913) | 0.978 | | |
| Alcoholic liver disease | 2.085 (1.099–3.955) | **0.024** | | |
| BMI | 0.958 (0.909–1.010) | 0.110 | | |
| MELD score | 1.208 (1.152–1.266) | **<0.001** | **1.125 (1.060–1.193)** | **<0.001** |
| History of OHE | 2.706 (1.346–5.440) | **0.005** | | |
| History of ascites or at study inclusion | 4.627 (2.042–10.485) | **<0.001** | | |
| Albumin | 0.826 (0.786–0.868) | **<0.001** | **0.888 (0.837–0.942)** | **<0.001** |
| Sodium | 0.794 (0.724–0.870) | **<0.001** | | |
| CHE | 3.876 (2.041–7.358) | **<0.001** | **2.032 (1.037–3.983)** | **0.039** |
| CFS (as a metric variable) | 1.910 (1.474–2.475) | **<0.001** | **1.534 (1.122–2.099)** | **0.007** |

Not significant on multivariable Cox regression models were alcoholic liver disease, a history of OHE, ascites and sodium.
Bold values indicates level of significance was defined as $P < 0.05$.
BMI, body mass index; CHE, covert hepatic encephalopathy; CFS, Clinical Frailty Scale; HR, hazard ratio; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy.

respective null hypothesis. However, because of the large number of tests, *P*-values should be interpreted with caution and in connection with effect estimates. Data were analyzed using IBM SPSS Statistic Version 23.0 (IBM, Armonk, NY) and R Version 3.4.2 (R Core Team, 2017, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

A total of 218 patients were prospectively enrolled in the outpatient cohort. Follow-up data were available for 200 patients, with a median follow-up time of 364 days (IQR 202–508). For the inpatient cohort, 99 consecutive hospitalized patients were prospectively enrolled. These patients were followed for a median of 28 days.

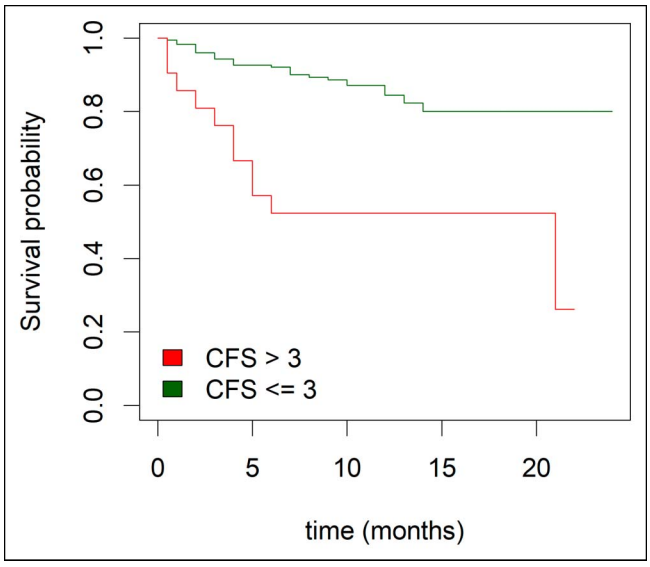


**Figure 1.** Impact of (pre)frailty (CFS > 3) on risk for death/need for liver transplantation in outpatients with liver cirrhosis. $P < 0.001$. CFS, Clinical Frailty Scale.

Baseline characteristics of both cohorts are displayed in Tables 1 and 3. In both cohorts, most patients were male (56.5% in the outpatient cohort and 65.7% in the inpatient cohort) and the most common etiology of underlying liver disease was chronic alcohol consumption (29.5% in the outpatient cohort and 70.7% in the inpatient cohort). The median MELD score was 10 (IQR 7–14) in the outpatient cohort and 17 (IQR 11–25) in the inpatient cohort.

### Predictors for the composite endpoint of death and liver transplantation (mortality) in the outpatient cohort

Given that all patients who had received a liver transplantation had done so because of final hepatic failure, they were treated as complete cases. In total, 39 patients died (n = 22) or received a liver transplantation (n = 17) during the follow-up. The frequency of deceased or transplanted patients was significantly higher in at least prefrail patients (CFS > 3) than in nonfrail patients (CFS ≤ 3) (Figure 1; log-rank $P < 0.001$). Univariable Cox regression analyses identified alcoholic liver disease, higher MELD score, history of OHE, presence of ascites, lower albumin, lower sodium, presence of CHE, and higher CFS as predictors of mortality (Table 2). In the multivariable Cox regression analysis, higher MELD score (hazard ratio [HR] 1.125, 95% confidence interval [CI] 1.060–1.193, $P < 0.001$), lower albumin (HR 0.888, 95% CI 0.837–0.942, $P < 0.001$), presence of CHE (HR 2.032, 95% CI 1.037–3.989, $P = 0.039$), and higher CFS (HR 1.534, 95% CI 1.122–2.099, $P = 0.007$) remained independently associated with higher mortality (Table 2). In addition, another multivariable Cox regression analysis was calculated including the aforementioned variables and CFS as a dichotomous variable (CFS > 3 vs CFS ≤ 3). Here, a CFS > 3 (HR 2.742, 95% CI 1.316–5.714, $P = 0.007$) remained independently associated with higher mortality.

To investigate the ability of the CFS to predict mortality irrespective of the amount of muscle mass, we analyzed a subcohort of 87

**Table 3. Demographics and clinical characteristics of the entire inpatient cohort and stratified by 28-day survival**

| Variable | All patients | Deceased 28-d | Alive 28-d | *P* value |
|---|---|---|---|---|
| n | 99 | 22 (22.2) | 77 (77.8) | |
| Age, yr (IQR) | 60 (52–66) | 57 (51–62) | 61 (52–68) | 0.195 |
| Male gender, n (%) | 65 (65.7) | 16 (72.7) | 49 (63.6) | 0.428 |
| Etiology | | | | |
| Alcohol, n (%) | 70 (70.7) | 19 (86.4) | 51 (66.2) | 0.277 |
| Viral hepatitis, n (%) | 0 (0) | 0 (0) | 0 (0) | |
| NAFLD, n (%) | 13 (13.1) | 2 (9.1) | 11 (14.3) | |
| Other/mixed, n (%) | 16 (16.2) | 1 (4.5) | 15 (19.5) | |
| Median MELD score (IQR) | 17 (11–25) | 26 (24–33) | 15 (10–21) | <0.001 |
| CP A/B/C, n (%) (before or at hospital admission) | 16/57/26 (16/58/26) | 1/13/8 (5/59/36) | 15/44/18 (20/57/23) | 0.176 |
| ACLF during hospital stay, n (%) | 39 (39.4) | 18 (81.8) | 21 (27.3) | <0.001 |
| History of ascites or at study inclusion, n (%) | 73 (73.7) | 17 (77.3) | 56 (72.7) | 0.669 |
| History of OHE, n (%) | 30 (30.3) | 14 (63.6) | 16 (20.8) | <0.001 |
| Albumin, g/L (IQR) | 26 (22–33) | 23 (20–26) | 28 (23–34) | 0.003 |
| Sodium, mmol/L (IQR) | 136 (133–139) | 134 (126–138) | 137 (133–139) | 0.030 |
| Infection during hospital stay, n (%) | 44 (44.4) | 16 (72.7) | 28 (36.4) | 0.002 |
| CFS (as a metric variable) | 3 (3–5) | 4 (3–5) | 3 (2–4) | 0.165 |
| CFS > 3 | 42 (42.4) | 11 (50.0) | 31 (40.3) | 0.415 |
| CFS > 4 | 26 (26.3) | 8 (36.4) | 18 (23.4) | 0.222 |
| TPMA below median[a] | | 9 (28.1) | 10 (31.3) | 0.784 |

Data are expressed as medians and IQRs or as frequencies and percentages.
ACLF, acute-on-chronic liver failure; CFS, Clinical Frailty Scale; CP, Child-Pugh; IQR, interquartile range; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; OHE, overt hepatic encephalopathy; TPMA, transverse psoas muscle area.
[a]Measured in 64 patients.

outpatients with available CT scans. The respective TPMA medians of the outpatient cohort were 666.18 $mm^2/m^2$ for men and 424.26 $mm^2/m^2$ for women. Baseline characteristics of this cohort are displayed in Supplementary Table 1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A310). In total, 33 patients of this cohort died or received a liver transplantation during the follow-up. Univariable Cox regression analyses identified alcoholic liver disease, higher MELD score, history of OHE, presence of ascites, lower albumin, lower sodium, presence of CHE, and higher CFS as negative predictors of mortality (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A310). Using the aforementioned variables and the variable low muscle mass (TPMA below the median vs TPMA above the median), we calculated a multivariable Cox regression analysis with stepwise variable selection. Here, higher MELD score, lower albumin, presence of CHE, and higher CFS (HR 1.553, 95% CI 1.127–2.141, $P = 0.007$) were independently associated with higher mortality (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A310). In addition, another multivariable Cox regression analysis was calculated including the aforementioned variables and the CFS as a dichotomous variable (CFS > 3 vs CFS ≤ 3). Here, a CFS > 3 (HR 2.783, 95% CI 1.277–6.065, $P = 0.010$) remained independently associated with higher mortality.

These findings remained unchanged even after forcing the variable low muscle mass into a Cox regression analysis with the 4 variables of MELD, albumin, presence of CHE, and CFS. Here, the CFS remained independently associated with higher mortality (HR 1.706, 95% CI 1.212–2.401, $P = 0.002$), whereas low muscle mass did not reach significance (HR 2.058, 95% CI 0.970–4.366, $P = 0.060$). In addition, another Cox regression analysis was conducted including the aforementioned variables and TPMA dichotomized according to quartiles (lowest quartile of muscle mass vs other 3 quartiles). Again, CFS remained independently associated with higher mortality (HR 1.606, 95% CI 1.181–2.184, $P = 0.003$), while the lowest quartile of muscle mass did not reach significance.

### Predictors for the composite of death and need for liver transplantation (mortality) in the inpatient cohort

Again, given that all patients who had received a liver transplantation had done so because of final hepatic failure, they were treated as complete cases. In total, 22 patients died (n = 20) or received a liver transplantation (n = 2) during a follow-up of 28 days. In univariate analyses, neither median CFS, at least pre-frailty (CFS > 3), nor frailty (CFS > 4) were associated with higher mortality rates at 28 days of the follow-up (Table 3). To identify predictors for higher short-term mortality (28 days) in

**Table 4. Analyses of potential predictors for the composite of death or need for liver transplantation (mortality) in patients of cohort 2 using multiple logistic regression models**

| | Model 1[a] | | Model 2[b] | | Model 3[c] | | Model 4[d] | |
|---|---|---|---|---|---|---|---|---|
| | OR | *P* value | OR | *P* value | OR | *P* value | OR | *P* value |
| ACLF during hospital stay | 14.911 (3.895–57.080) | <0.001 | 24.243 (4.970–118.262) | <0.001 | 12.800 (2.193–74.724) | 0.005 | 21.452 (4.655–98.862) | <0.001 |
| Albumin | 0.916 (0.846–0.992) | 0.030 | 0.911 (0.839–0.989) | 0.025 | 0.917 (0.843–0.997) | 0.043 | 0.908 (0.834–0.988) | 0.025 |
| Infections during hospital stay | 5.839 (1.601–21.293) | 0.008 | 7.972 (1.865–34.079) | 0.005 | 6.565 (1.505–28.631) | 0.012 | 6.555 (1.663–25.841) | 0.007 |
| Frailty (CFS > 4) | | | 4.627 (1.036–20.662) | 0.045 | 4.351 (0.946–20.007) | 0.059 | | |
| MELD | | | | | 1.067 (0.976–1.166) | 0.152 | | |
| CFS (as a metric variable) | | | | | | | 1.475 (0.947–2.298) | 0.086 |

[a]Model 1: logistic regression model with stepwise variable selection. Not significant were: MELD, history of overt hepatic encephalopathy, sodium and clinical frailty scale.
[b]Model 2: logistic regression model including the variables: ACLF, albumin, infections, frailty.
[c]Model 3: logistic regression model including the variables: ACLF, albumin, infections, frailty, MELD.
[d]Model 4: logistic regression model including the variables: ACLF, albumin, infections, CFS.
ACLF, chronic liver failure; CFS, clinical frailty scale; MELD, model for end-stage liver disease; OR, odds ratio.

our inpatient cohort, we conducted different logistic regression analyses (Table 4). At first, a logistic regression model with stepwise variable selection was conducted including all univariable significant factors ($P < 0.05$) as displayed in Table 4. Here, ACLF (HR 14.911, 95% CI 3.895–57.080, $P < 0.001$), lower albumin (HR 0.916, 95% CI 0.846–0.992, $P = 0.030$), and the presence of infection during the hospital stay (HR 5.839, 95% CI 1.601–21.293, $P = 0.008$) remained independently associated with higher mortality (Table 4). Additionally, another logistic regression model was calculated including the aforementioned variables and the CFS as a dichotomous variable (CFS > 4 vs CFS ≤ 4). Although in univariate analysis no significant difference in frequency of frailty between deceased and alive patients could be found, on logistic regression analysis frailty (CFS > 4) remained significantly associated with higher mortality even after controlling for ACLF, albumin, and the presence of infection (HR 4.627, 95% CI 1.036–20.662, $P = 0.045$) (Table 4). When including the MELD score into this model, there remained a clear trend between frailty and higher mortality (odds ratio [OR] 4.351, 95% CI 0.946–20.007, $P = 0.059$) (Table 4). The CFS as a metric variable did not reach significance in a model including ACLF, lower albumin, and presence of infection (OR 1.475, 95% CI 0.947–2.298, $P = 0.086$) (data not shown).

To investigate the ability of the CFS to predict mortality irrespective of the amount of muscle mass, we analyzed the subcohort of 64 inpatients with available CT scans. The respective TPMA medians of the inpatient cohort were 483.88 $mm^2/m^2$ for men and 333.27 $mm^2/m^2$ for women. In this cohort, 19 patients died within the median of 28 days of follow-up. We conducted a logistic regression including the variables presence of ACLF, lower albumin, presence of infection, presence of frailty, and lower muscle mass (TPMA above vs below the median). Here, frailty (CFS > 4) was not significantly associated with higher mortality at 28 days of the follow-up (HR 2.769, 95% CI 0.535–14.331, $P = 0.225$) (see Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/CTG/A310).

## DISCUSSION

In this study, we could demonstrate in a large cohort of German patients with liver cirrhosis that the CFS is a suitable tool for risk stratification of outpatients regarding medium-term mortality or need for liver transplantation. This finding was independent of the underlying amount of muscle mass (reflecting sarcopenia). In addition, frailty as defined by a CFS > 4 seems to be associated with higher short-term mortality (28 days) in nonelectively hospitalized patients with liver cirrhosis. This highlights that the diagnosis, treatment, and prevention of frailty seems to be of high importance to improve the prognosis in these patients.

Recently, measures of frailty or sarcopenia have been proposed as useful independent predictors for liver-related death, especially in patients on the waiting list for liver transplantation (4,19). In a study conducted by Lai et al. (20), frailty defined by the more complex Liver Frailty Index was independently associated with higher mortality in these patients. Tandon et al. (9) were the first to compare the usefulness of CFS with 2 other more time-consuming measures of frailty (the Short Physical Performance Battery and the Fried Frailty criteria) in a total of 300 outpatients with liver cirrhosis. Here, the predictive ability of CFS regarding a composite endpoint of unplanned hospitalization and mortality was comparable to both other tests. Although parts of our findings are more or less in line with the study conducted by Tandon et al., there is a major difference regarding the primary endpoint between both studies. In the Canadian study, a composite endpoint of unplanned hospitalization and mortality was used and only 19 of 300 patients died and 13 were hospitalized for liver transplantation. Our study focused on the combined endpoint of death/liver transplantation and adds important value by demonstrating a robust association between higher frailty according to the CFS and worse prognosis. To the best of our knowledge, our study is the first to demonstrate

that the predictive value of the CFS is independent of the amount of muscle mass (reflecting sarcopenia) in outpatients with liver cirrhosis. This finding is most likely explained by the fact that frailty is a multifactorial construct and only partially caused by the loss of muscle mass. Although there is a correlation between the amount of muscle mass as measured by CT indices and frailty indices, Tapper et al. (21) demonstrated that especially in women there is a comparable correlation between cognitive function and frailty. This emphasizes that frailty is a multifactorial construct defined not only by muscle quantity but also muscle functionality, cognitive impairment, comorbidities, and aging. Low muscle mass may be one part and a driving force for emerging frailty but considered individually it might not necessarily have to correspond to frailty (22). Therefore, in the context of an outpatient setting, where CT scans are often not readily available, the CFS seems to be a useful, complementary tool to established liver-related scores such as MELD or CP to identify patients with higher risk for mortality.

A second important finding of our study is the observation that frailty seems to be associated with higher short-term mortality (28 days) in nonelectively hospitalized patients with liver cirrhosis. However, there was only a trend for a dose response for the CFS (OR 1.475, $P = 0.086$), and we failed to demonstrate an independent association between the predictive value of the CFS and a lower amount of muscle mass in inpatients. Nevertheless, this is most likely explained by a type II error, and we believe that when investigating larger cohorts there will be a significant dose response between CFS and higher short-term mortality.

To the best of our knowledge, our study is the first to investigate the predictive value of CFS in hospitalized patients with liver cirrhosis. However, the usefulness of the CFS has been investigated in older patients without liver cirrhosis treated on intensive care units. Fernando et al. (23) could demonstrate in a large cohort of 1,510 elderly patients with infections that the presence of frailty (CFS $>$ 4) is associated with increased mortality. In addition, frailty was associated with extubation failure, need for tracheostomy and higher hospital mortality in patients with the need for invasive mechanical ventilation (24). Tapper et al. (25) investigated the usefulness of standard assessments of frailty such as the Braden Scale or the activity of daily living for the prediction of 90-day mortality in hospitalized patients with liver cirrhosis. Here, they could demonstrate that both measures were associated with higher mortality, although they failed to demonstrate an association between frailty and the 30-day readmission rate. Our findings can be interpreted in the context of the aforementioned studies. Especially, patients with ACLF suffer from an end-stage form of liver cirrhosis (15). As recently demonstrated in large multicenter studies, the prognosis of hospitalized patients with liver cirrhosis is mainly determined by liver function, extrahepatic organ failures, and the presence of infections (26,27). Our data support the assumption that the physical reserve or frailty as expressed by the CFS is an additional important determinant for survival in life-threatening situations such as ACLF. This hypothesis is supported by studies conducted in critically ill patients with sepsis treated on intensive care units. Here, the evidence is strong that frailty is closely linked to higher mortality (23,24). Nevertheless, it is obvious that our findings need to be validated in larger prospective multicenter trials before final conclusions can be drawn.

Our study has some limitations that have to be acknowledged. First, both cohorts with available CT scans are relatively small and our results are therefore prone for a type II error. However, especially in the outpatient cohort, this only strengthens our findings that higher scores in the CFS are associated with higher mortality, independent of the respective amount of muscle mass. Nevertheless, larger multicenter studies are needed to strengthen and validate our findings. Especially, the generalizability of our outpatient cohort is limited by several exclusion criteria. Because this cohort was mainly recruited for studies on CHE, we excluded patients with e.g., electrolyte disorders, transjugular intrahepatic portosystemic shunt, or preterminal comorbidities (14). Therefore, our results may not be generalizable to all patients with liver cirrhosis. Last, we assessed the CFS only at baseline. Therefore, we cannot assess the impact of changes in the CFS on the prediction of mortality. Future studies should especially focus on the sensitivity of the CFS to measure the effectiveness of interventions to improve frailty.

In conclusion, our study demonstrates that the CFS is an easy-to-use, valid, and universally available tool for the risk stratification of outpatients with liver cirrhosis regarding medium-term mortality or need for liver transplantation independent of the amount of muscle mass. Thus, regular testing with the CFS may lead to an improvement of care in patients with liver cirrhosis. In addition, frailty seems to be associated with higher short-term mortality (28 days) in nonelectively hospitalized patients with liver cirrhosis.

### CONFLICTS OF INTEREST

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## Study Highlights

### WHAT IS KNOWN

- ✓ Frailty is common in patients with liver cirrhosis.
- ✓ Data from other countries outside of Canada regarding the ability of the CFS to predict mortality are lacking.

### WHAT IS NEW HERE

- ✓ CFS was independently associated with higher mortality in European outpatients with liver cirrhosis.
- ✓ The association between CFS and mortality remained after controlling for muscle mass in outpatients.
- ✓ Frailty (CFS $>$ 4) was an independent predictor for 28-day mortality in inpatients.

### TRANSLATIONAL IMPACT

- ✓ Especially in outpatients, CFS is a useful predictor regarding increased mortality independent of muscle mass.

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