



Liver, Pancreas and Biliary Tract

Higher scores in the Clinical Frailty Scale are associated with covert and overt hepatic encephalopathy in patients with cirrhosis

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ABSTRACT

Background: Frailty increases the vulnerability to internal and external stressors and may therefore be an indicator of a higher frequency of cirrhosis complications. We aimed to investigate the association of the Clinical Frailty Scale (CFS) with covert (CHE) and overt HE (OHE) development in patients with cirrhosis. **Methods:** This study analyzed data of 228 patients with cirrhosis. Frailty was assessed using CFS. Patients were examined for the presence of CHE (using PHES) at study inclusion and followed for OHE.

Results: Median CFS was 3 and 26 (11 %) patients were at least pre-frail (CFS > 3). In multivariable logistic regression analysis in patients without a history of OHE ($n = 195$), a higher CFS was associated with the presence of CHE at baseline (OR 1.6, $p = 0.039$). During follow-up, 42 (18 %) patients developed an episode of OHE. In multivariable competing risk regression analyses, a higher CFS was independently associated with the development of an OHE episode in the total cohort (sHR 1.97, $p < 0.001$) and in the subcohort of patients without a history of OHE (sHR 1.88, $p = 0.008$).

Conclusion: CFS appears to be a reliable tool to identify patients at higher risk of HE in whom intensified monitoring and treatment may be justified.

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1. Introduction

Liver cirrhosis is widely prevalent worldwide and caused 1.32 million deaths in 2017 [1]. Hepatic encephalopathy (HE) represents one of the most severe complications of cirrhosis. HE can be roughly divided into two grades termed covert (CHE) and overt HE (OHE) [2]. While CHE is an umbrella term combining the two lowest grades of HE - minimal HE and HE grade 1 according to the West-Haven-Criteria -, OHE covers the grades 2–4 according to West-Haven. The prevalence of MHE is heavily dependent on disease stages and ranges from <20 % in patients with Child-Pugh A (CP) cirrhosis to >50 % in patients with CP C. The incidence rates of OHE are less well studied and are approximately 10 % and 25 % per year in patients with CP A and B cirrhosis, respectively [3]. The occurrence of OHE and even the presence of CHE can be seen as an indicator of poorer prognosis and heavily affect patients' well-

being [4,5]. Therefore, it is of pivotal importance to evaluate potentially modifiable factors to identify patients at high risk for HE and subsequently prevent its occurrence.

Frailty is common in patients with cirrhosis and defined as a syndrome of decreased resistance to stressors and a multifactorial construct of a cumulative decline of physiologic reserve [6]. Consequently, the presence of frailty is an indicator of poorer prognosis regardless of the presence of various complications of cirrhosis [7]. The pathophysiology of frailty is complex and its occurrence is aggravated by sarcopenia, cognitive decline and cirrhosis complications [8]. All these factors suggest frailty as a plausible risk factor for HE in patients with cirrhosis. Therefore, the aims of this study were to investigate the association between frailty defined by the easily applicable Clinical Frailty Scale (CFS) and the presence of CHE as well as the development of OHE in a well-characterized cohort of patients with cirrhosis.

2. Methods

2.1. Patient cohort

In total, 240 patients with cirrhosis were recruited for this prospective cohort study between March 2017 and December 2019

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at the Cirrhosis Center Mainz (CCM) of the University Medical Center of the Johannes Gutenberg-University in Mainz, Germany. 12 patients were lost to follow-up. All patients were either recruited in the outpatient department of the CCM or during elective hospitalization. Reasons for elective hospitalization were either to perform liver biopsy, paracentesis (without evidence of spontaneous bacterial peritonitis), esophagogastroduodenoscopy with expected band ligation or evaluation for liver transplantation. Detailed characteristics of this study have also been published elsewhere [9,10].

The leading etiology of the underlying liver disease was determined according to clinical, serological and histological findings. Diagnosis of cirrhosis was established by histology or a combination of conclusive appearance in ultrasound, radiological imaging, endoscopic features of portal hypertension, and medical history. Blood biochemistry was assessed in all patients. Patients were not approached for this study and subsequently not included into the database, if they fulfilled one or more of the following criteria: evidence of an active infection, chronic alcohol consumption during the last three months, any intake of psychotropic drugs or opioids, the presence of pre-terminal comorbidities (heart disease NYHA III-IV, chronic obstructive pulmonary disease Gold C and D, renal failure with creatinine > 1.5 mg/dl), the presence of hepatocellular carcinoma (HCC) or other malignancies, transjugular intrahepatic portosystemic shunt (TIPSS), neurological comorbidities (i.e. dementia or history of stroke), history of recent head-trauma, and severe electrolyte disorders (serum sodium < 130 mg/dl or > 150 mg/dl). Patients with a history of OHE were allowed to participate in the study, if they were on consequent and stable treatment with lactulose and/or rifaximin.

2.2. Assessment of frailty

The CFS was used to assess frailty. Here, disease symptoms, loss of function, cognitive impairment, and life expectancy are considered in a structured manner, which is described in detail elsewhere [11,12]. The CFS is based on clinical assessment and divided into 9 categories (1: very fit, 2: well, 3: well with treated comorbid diseases, 4: apparently vulnerable/pre-frail, 5: mildly frail, 6: moderately frail, 7: severely frail, 8: very severely frail, and 9: terminally ill) [11]. According to accepted definitions, pre-frailty was defined as a CFS > 3 (CFS 4–9) and frailty was defined as a CFS > 4 (CFS 5–9).

2.3. Diagnosis of HE

First, every patient was examined by an experienced hepatologist to rule out OHE. The presence of HE grade 1 was diagnosed after detailed neurological examination according to the West-Haven criteria [2].

Testing for MHE was done using the portosystemic encephalopathy (PSE) syndrome test, which yields the psychometric hepatic encephalopathy score (PHES). Interpretation of PHES was done as previously described with German norms [13]. PHES was never performed on the same day of any other intervention to exclude potential confounding factors. All tests were performed in a quiet, lighted room between 09.00 a.m. and 04.00 p.m.. A score < -4 was considered pathological [13].

In addition, a subcohort of 217 patients was tested with the Animal Naming Test (ANT), as also described elsewhere [14]. For the ANT, patients were asked to name as many animals as possible in one minute. Repeats and errors are excluded from the calculations. The number of named animals after one minute is defined as the score. To compensate for the influence of age and education on the results in ANT, we calculated the S-ANT1 which has been proposed by Campagna et al. [15].

2.4. Determination of IL-6 and ammonia serum levels

IL-6 serum levels were determined in a subset of patients at the day of study inclusion immediately after testing with PHES using a commercially available Chemiluminescence immunoassay (CLIA) (Cobas e 411 Analyzer, F. Hoffmann-La Roche AG, Basel, Swiss).

Venous ammonia levels were measured according to a standard operating procedure that involved rapid sample transport on ice to the laboratory within five minutes and the upper limit of normal (ULN) was 72 $\mu\text{mol/l}$.

2.5. Follow-up evaluation

All patients were followed during routine visits every six months in the outpatient clinic of the Cirrhosis Center Mainz, as described elsewhere [4]. At each visit or during unplanned hospitalizations, each patient was examined by an experienced hepatologist to rule in or rule out OHE. Additionally, every patient was asked for hospitalizations in other hospitals. The presence of OHE was diagnosed after a detailed neurological examination according to the West-Haven criteria. In patients with available follow-up, no OHE episode occurred that was treated outside of our center, or in case of hospitalization, patients were transferred to our center for further management. Moreover, patients were followed for the occurrence of the composite endpoint of death or requirement for liver transplantation. Patients who required liver transplantation were considered as complete cases given that all patients were transplanted because of a high MELD score and none because of HCC.

2.6. Ethics

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (Nr. 837.232.17 [11066]). Written informed consent was obtained from all participants.

2.7. Statistical analysis

Data were analyzed using IBM SPSS Statistic Version 27.0 (Armonk, NY: IBM Corp.), GraphPad Prism Version 8.0.2 (GraphPad Software, California, US) and R 4.1.3 (R Core Team (2022)). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Quantitative data are expressed as medians with interquartile ranges (IQR) and pairwise comparisons for quantitative variables were performed with an unpaired *t*-test or with the Mann-Whitney U Test. Categorical variables are expressed as frequencies and percentages. For comparison of two or more patient groups, a chi-square test was applied. Correlation analyses between two metric variables were performed using Spearman's rank correlation.

To identify variables associated with the presence of CHE defined by PHES at baseline, various multivariable logistic regression models were conducted including univariable significant variables. Additionally, multivariable linear regression analyses were conducted to identify variables associated with poorer results in S-ANT1.

To identify variables associated with the development of OHE during follow up, univariable and multivariable Cox regression models were conducted. These models were based on a stepwise variable selection procedure or using the inclusion method with predefined variables, as indicated. To solidify the results of these models, we also conducted multivariable Cox regression models to identify variable associated with the development of the endpoint of OHE and transplantation-free survival. Moreover, given

Table 1

Demographics and clinical characteristics of the total cohort, patients with covert hepatic encephalopathy (CHE) and patients without CHE at the time of study inclusion.

Variable	All patients n = 228	Patients with CHE n = 71	Patients without CHE n = 157	p-value
Age, y (IQR)	60 (53; 66)	62 (54; 69)	59 (53; 65)	0.209
Male gender, n (%)	129 (56.6)	46 (64.8)	83 (52.9)	0.093
Aetiology				0.172
Alcohol, n (%)	74 (32.5)	30 (42.3)	44 (28.0)	
Viral hepatitis, n (%)	45 (19.7)	12 (16.9)	33 (21.0)	
NAFLD, n (%)	29 (12.7)	9 (12.7)	20 (12.7)	
Cholestatic/	31 (13.6)	5 (7.0)	26 (16.6)	
Autoimmune, n (%)	49 (21.5)	15 (21.1)	34 (21.7)	
Other/mixed, n (%)				
Median MELD score (IQR)	10 (8; 14)	13 (8; 17)	10 (7; 13)	<0.001
Child-Pugh A/B/C, n (%)	138/69/21 (60.5/30.3/9.2)	26/31/14 (36.6/43.7/19.7)	112/38/7 (71.3/24.2/4.5)	<0.001
History of ascites, n (%)	117 (51.3)	45 (63.4)	72 (45.9)	0.014
History of OHE, n (%)	33 (14.5)	22 (31.0)	11 (7.0)	<0.001
Varices, n (%)	135 (59.2)	47 (66.2)	88 (56.1)	0.149
Sodium, mmol/l (IQR)	139 (137; 140)	138 (135; 140)	139 (137; 140)	0.088
Albumin, g/l (IQR)	34 (29; 38)	30 (25; 37)	35 (31; 38)	<0.001
Bilirubin, mg/dl (IQR)	1.2 (0.8; 2.3)	1.5 (0.8; 3.0)	1.2 (0.8; 2.1)	0.083
WBC, /nl (IQR)	5.5 (4.2; 7.3)	5.6 (4.5; 7.7)	5.5 (4.0; 7.2)	0.282
Ammonia, μ mol/l (IQR)*	47 (37; 59)	47 (34; 65)	47 (37; 57)	0.753
Interleukin 6, pg/ml (IQR)**	8 (5; 21)	14 (7; 43)	7 (5; 13)	<0.001
CHE, n (%)	71 (31.1)	71 (100)	0 (0)	N/A
S-ANT1 (IQR)***	20 (17; 25)	16 (12; 20)	23 (19; 26)	<0.001
CFS (IQR)	3 (2; 3)	3 (3; 3)	3 (2; 3)	<0.001

Data are expressed as medians and interquartile ranges or as frequencies and percentages; NAFLD, non-alcoholic fatty liver disease; MELD, model for end-stage liver disease; CHE, covert hepatic encephalopathy; S-ANT1, simplified animal naming test; CFS, clinical frailty scale.

- * Available in 209 patients.
- ** Available in 211 patients.
- *** Available in 217 patients.

the competing nature of death/transplantation regarding the risk for development of OHE, we repeated multivariable analyses using the method of Fine and Gray and treated death/transplantation as competing events. Additionally, we compared the cumulative OHE incidences in patients with and without pre-frailty by cumulative incidence plots. Thereby, we used competing risk methodology where death and transplantation were considered as competing events for OHE. Here, statistical significance was tested using Gray's Test. For these analyses, the R package [tidycmprsk] was used.

To investigate the discriminative ability of CFS to identify patients developing OHE within the next 180 days of follow-up, we calculated the area under the receiver operating characteristic curve (AUROC) and its respective 95 % confidence interval (CI). To identify the ideal cut-off for CFS, the Youden-Index was determined.

Last, to compare IL-6 and ammonia serum levels between patients with and without prefrailty, we conducted a 1:1 matching procedure to obtain comparable groups. Patients were matched for age, gender, alcoholic etiology of cirrhosis, MELD, CP stage, history of ascites, history of OHE, sodium, albumin and CHE status.

For all tests, we used a 0.05 level to define statistically relevant deviations from the respective null hypotheses. Given that our complete data analysis is exploratory, *p*-values have to be interpreted in the context of the design and no adjustments for multiple testing were performed.

3. Results

3.1. Demographics and baseline characteristics

Data of 228 patients were analyzed and the baseline characteristics of this cohort are displayed in Table 1. At baseline, CHE was detected in 71 (31.1 %) patients. Median age was 60 years (IQR

53; 66) and the majority of patients had Child-Pugh A cirrhosis (60.5 %) with a median MELD score of 10 (IQR 8; 14).

3.2. Variables associated with the presence of CHE at baseline

Univariable comparisons between patients with and without CHE are displayed in Table 1. Both groups differed significantly in terms of median MELD score, Child-Pugh grade, history of ascites and OHE, albumin serum levels and CFS. The median and distribution of CFS in the groups of patients with and without CHE are displayed in Fig. 1A (*p* < 0.001). Fig. 1B displays the comparison of CFS in patients with a history of OHE, CHE and patients without HE. Patients with a history of OHE or CHE had a significantly higher median CFS (*p* < 0.05 each) compared to patients without HE, while there was no significant difference in CFS between patients with a history of OHE and CHE.

To identify variables associated with the presence of CHE at baseline, multivariable logistic regression models were conducted including variables with a *p* < 0.05 in univariable analyses. In a model including the total cohort, only history of OHE was associated with the presence of CHE (OR 4.150, 95 % CI 1.760–9.785, *p* = 0.001), while CFS, MELD score, albumin or history of ascites were not (Table 2). The same multivariable model was fitted in the subcohort of patients without a history of OHE (*n* = 195). Here, a higher CFS (OR 1.648, 95 % CI 1.056–2.570, *p* = 0.027) was the only variable associated with the presence of CHE, while MELD score, albumin and history of ascites were not.

A subcohort of 217 patients was also tested with S-ANT1. There was a moderate correlation between results in PHEs and S-ANT1 (ρ = 0.531, *p* < 0.001). To identify variables associated with poorer results in S-ANT1, multivariable linear regression models were fitted including the aforementioned variables. Here, a higher CFS was associated with poorer results in S-ANT1 (β = -0.196, *p* = 0.006) in the total cohort as well as in the subcohort of pa-

Table 2
Variables associated with the presence of covert hepatic encephalopathy using multivariable logistic regression models.

	Multivariable logistic regression analysis (total cohort)		Multivariable logistic regression analysis (subcohort of patients without a history of OHE, n = 195)	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
MELD score	1.075 (0.996–1.160)	0.063	1.071 (0.986–1.164)	0.105
Albumin	0.974 (0.916–1.037)	0.411	1.000 (0.934–1.072)	0.993
CFS	1.320 (0.916–1.902)	0.136	1.648 (1.056–2.570)	0.027
History of OHE	4.150 (1.760–9.785)	0.001		
History of ascites	0.921 (0.453–1.869)	0.819	1.339 (0.622–2.879)	0.455

The multivariable logistic regression models were performed with an inclusion variable selection procedure and all univariable significant variables (from Table 1) were included into the models.

OR, odds ratio; 95 % CI, 95 % confidence interval; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; CFS, clinical frailty scale.

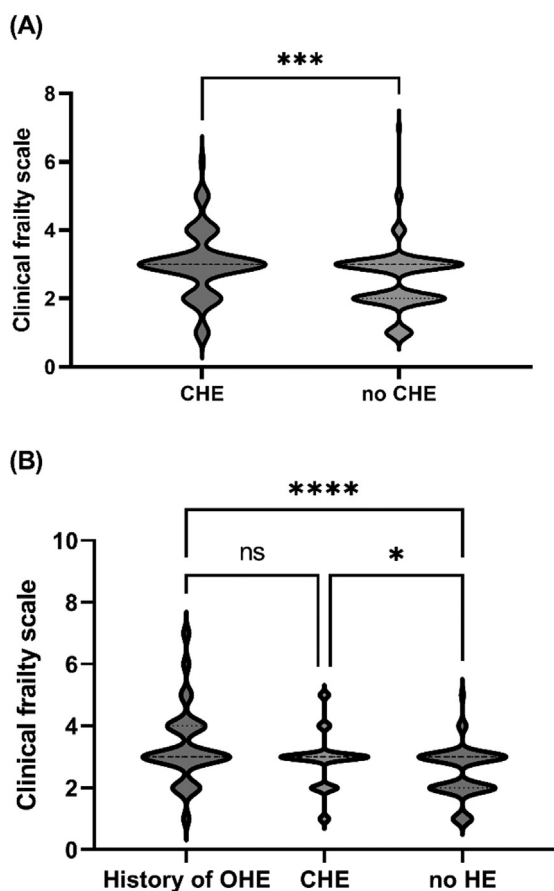


Fig. 1. A. Comparison of CFS in patients with and without hepatic encephalopathy (HE). Fig. 1A displays the violin plots of the distribution of CFS in patients with and without CHE ($***p < 0.001$). Fig. 1B displays the violin plots of the distribution of CFS in patients with a history of OHE, patients with CHE but no history of OHE and patients without HE ($*p < 0.05$, $****p < 0.0001$).

patients without a history of OHE ($\beta = -0.196$, $p = 0.010$) (supplementary Table 1).

3.3. Variables associated with the development of OHE during follow-up

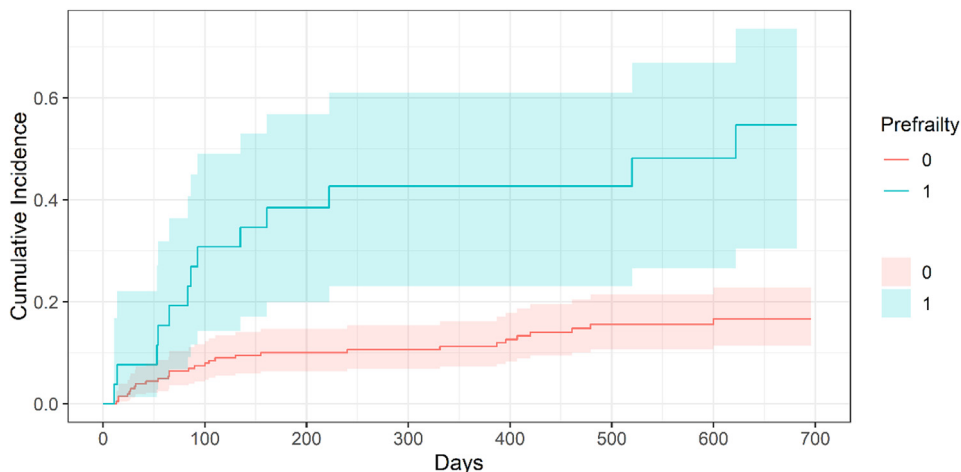
All patients were followed for the development of the first OHE episode or death/liver transplantation. Median follow-up time was 588 (IQR 371–745) days. During follow-up a total of 42 (18.4 %) first episodes of OHE occurred. The distribution of the OHE grade according to the West-Haven Criteria was as follows: 31 (73.8 %) grade 2, 9 (21.4 %) grade 3, 2 (4.8 %) grade 4. The triggers of the

OHE episodes were infections (31 %), upper gastrointestinal bleeding (10 %), constipation (5 %), electrolyte disorders (5 %) or multiple factors (19 %). In 13 patients (31 %) no precipitating factor could be identified. In total, 22 patients (9.6 %) died or received a liver transplantation before an episode of OHE and 30 (13.2 %) patients died or received a liver transplantation after an episode of OHE. Cumulative OHE-incidences differed significantly between patients with at least pre-frailty (CFS > 3) and patients with CFS ≤ 3 ($p < 0.001$, Fig. 2). The cumulative OHE-incidences for patients with CFS > 3 at 3, 6 and 12 months were 27 % (95 % CI 12; 45), 38 % (20; 57) and 43 % (23; 62), respectively. For patients with CFS ≤ 3 the cumulative OHE-incidences were 7.5 % (4.4; 12), 10 % (6.3; 15) and 11 % (7.3; 16) at 3, 6 and 12 months, respectively.

To identify variables associated with the development of OHE during follow-up, univariable Cox regression analyses were conducted in a first step. These results are displayed in Table 3. To identify variables independently associated with the development of OHE, a multivariable Cox regression model was fitted using a stepwise variable selection procedure under consideration of all univariable significant variables. Here, a higher CFS, a higher MELD score, lower albumin levels and CHE at baseline were associated with development of OHE (Model 1, Table 3). The independent association between a higher CFS and OHE development was validated in a confirmatory multivariable regression analysis using the method of Fine and Gray (Model 3, Table 3). In a second multivariable Cox regression model using the same procedure pre-frailty (CFS > 3, ref. CFS ≤ 3) was included as a dichotomous variable instead of CFS as a metric variable (Model 2, Table 3). Here, pre-frailty (CFS > 3) was independently associated with developing OHE during follow-up (HR 2.892, $p = 0.002$). In a separate model including frailty (CFS > 4, ref. CFS ≤ 4) as a dichotomous variable (HR 3.407, $p = 0.012$) the association was even stronger (supplementary Table 2). To identify variables associated with the development of a first OHE episode during follow-up, we excluded all patients with a history of OHE from the cohort. In the remaining subcohort ($n = 195$), a higher MELD score, lower albumin levels and a higher CFS were independently associated with a first episode of OHE (Table 4). Again, the independent association between a higher CFS and development of a first OHE episode was validated in a confirmatory multivariable regression analysis using the method of Fine and Gray (Model 2, Table 4).

To analyze the discriminative ability of CFS to predict the development of an OHE episode ($n = 30$ events) during the next 180 days of follow-up, a ROC curve was conducted. Here, the AUROC was 0.75 (95 % CI 0.66; 0.83). The ideal cut-off was a CFS of ≥ 3 (sensitivity: 93 %, specificity: 42 %).

To identify variables associated with the development of the composite endpoint of OHE and transplantation-free survival, univariable Cox regression analyses were conducted, which are displayed in supplementary Table 2. Following, a multivariable Cox



	0	100	200	300	400	500	600	700
0								
At Risk	202	179	157	140	117	98	73	59
Events	0	16	20	21	24	28	29	29
1								
At Risk	26	15	10	9	8	7	5	2
Events	0	8	10	11	11	11	12	13

Fig. 2. Cumulative overt hepatic encephalopathy incidences for patients with and without pre-frailty (CFS > 3 vs. CFS ≤ 3, *p* < 0.001). The colored areas display the 95 % confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Variables associated with the development of overt hepatic encephalopathy in the total cohort using univariable and multivariable Cox regression models as well as a Fine and Gray regression model.

	Univariable Cox regression analysis		Multivariable Cox regression analysis		Multivariable Cox regression analysis		Multivariable regression analysis using the Fine and Gray method	
	HR (95 % CI)	<i>p</i> -value	Model 1 HR (95 % CI)	<i>p</i>	Model 2 HR (95 % CI)	<i>p</i>	Model 3 sHR (95 %CI)	<i>p</i>
Age in years	1.002 (0.974–1.031)	0.880						
Male gender (ref.: female gender)	1.397 (0.743–2.627)	0.300						
MELD score	1.195 (1.144–1.247)	<0.001	1.112 (1.049–1.179)	<0.001	1.108 (1.044–1.177)	<0.001		ns
History of OHE	2.915 (1.462–5.814)	0.002		ns		ns		ns
History of ascites	4.774 (2.209–10.320)	<0.001		ns		ns		ns
Sodium	0.754 (0.687–0.827)	<0.001		ns		ns		ns
Albumin	0.803 (0.762–0.846)	<0.001	0.874 (0.822–0.930)	<0.001	0.863 (0.811–0.918)	<0.001	0.91 (0.85–0.98)	0.017
CHE	3.459 (1.881–6.360)	< 0.001	2.025 (1.069–3.835)	0.030	1.974 (1.040–3.745)	0.037		ns
CFS	2.647 (1.981–3.538)	<0.001	2.104 (1.504–2.945)	<0.001			1.97 (1.35–2.89)	<0.001
Pre-frailty (CFS > 3)	4.811 (2.493–9.284)	<0.001			2.892 (1.454–5.753)	0.002		

The multivariable Cox regression model were performed with a stepwise variable selection procedure. Model 1: not significant and therefore not included into the final model were the following variables: Sodium (*p* = 0.870), history of ascites (*p* = 0.839), history of OHE (*p* = 0.827).

Model 2: not significant and therefore not included into the final model were the following variables: Sodium (*p* = 0.749), history of ascites (*p* = 0.797), history of OHE (*p* = 0.824).

Model 3: The multivariable regression analysis using the Fine and Gray method was performed with a predefined inclusion variable selection. Only significant variables are displayed. Not significant were: CHE (*p* = 0.12), sodium (*p* = 0.4), history of ascites (*p* = 0.5), history of OHE (*p* = 0.2) and MELD (*p* = 0.3).

HR, hazard ratio; sHR: subdistribution hazard ratio; 95 % CI, 95 % confidence interval; ns, not significant; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; CHE, covert hepatic encephalopathy; CFS, clinical frailty scale.

Table 4

Variables associated with the development of overt hepatic encephalopathy in the subcohort of patients without a history of OHE ($n = 195$) using multivariable Cox regression models.

	Multivariable Cox regression analysis		Multivariable regression analysis using the Fine and Gray method	
	Model 1		Model 2	
	HR (95 % CI)	<i>p</i> -value	sHR (95 % CI)	<i>p</i> -value
MELD score	1.071 (1.000–1.147)	<0.001		
Albumin	0.824 (0.757–0.897)	<0.001	0.85 (0.78–0.93)	<0.001
CFS	1.817 (1.171–2.818)	0.008	1.88 (1.18–2.99)	0.008

Model 1: The multivariable Cox regression model was performed with a stepwise variable selection procedure. Not significant and therefore not included into the final model were the following variables: CHE ($p = 0.064$), sodium ($p = 0.273$) and history of ascites ($p = 0.637$).

Model 2: The multivariable regression analysis using the Fine and Gray method was performed with a predefined inclusion variable selection. Only significant variables are displayed. Not significant were: CHE ($p = 0.2$), sodium ($p = 0.5$), history of ascites ($p = 0.6$) and MELD ($p = 0.4$).

HR, hazard ratio; sHR, subdistribution hazard ratio; 95 % CI, 95 % confidence interval; ns, not significant; MELD, model for end-stage liver disease; CHE, covert hepatic encephalopathy; CFS, clinical frailty scale.

regression model was fitted based on a stepwise variable selection procedure including all univariable significant variables. Here, a higher CFS (HR 1.636, 95 % CI 1.234–2.171, $p < 0.001$), a higher MELD score (HR 1.092, 95 % CI 1.041–1.146, $p < 0.001$), lower albumin levels (HR 0.884, 95 % CI 0.840–0.930, $p < 0.001$) and CHE at baseline (HR 1.730, 95 % CI 1.025–2.921, $p = 0.040$) were independently associated with poorer OHE and liver transplantation free survival (supplementary Table 3).

3.4. Analyses of the association between pre-frailty (CFS > 3) and IL-6 serum levels or ammonia

To address potential pathophysiological aspects of the association between a CFS > 3 (at least pre-frailty) and HE, we aimed to compare serum levels of IL-6 and ammonia between patients with a CFS > 3 and ≤ 3 . IL-6 and ammonia serum levels were available in 211 and 209 patients, respectively. In the group of patients with both measures available, we conducted a 1:1 matching procedure between patients with a CFS > 3 and ≤ 3 . After matching, both groups consisted of 21 patients and were well balanced (supplementary Table 4). Patients with a CFS > 3 had significantly higher levels of IL-6 (38 vs. 28 pg/ml, $p = 0.043$) and ammonia (51 vs. 37 $\mu\text{mol/l}$, $p = 0.041$) compared to patients with a CFS ≤ 3 (supplementary Figure 1).

4. Discussion

Identifying patients at high risk for HE development is important in clinical practice. In this study, we were able to demonstrate that (pre-)frailty, quantified by CFS, is associated with the presence of CHE in patients without a history of OHE. Moreover, we found that a higher CFS is strongly associated with OHE development irrespective of the presence of CHE at baseline. As demonstrated in a matched subcohort, the higher frequency of HE in patients with a higher CFS may be explained by elevated levels of ammonia and systemic inflammation.

Frailty is common in patients with cirrhosis; however, the prevalence varies considerably according to the used test. In this study, we used the easily applicable CFS, which has been proven to be comparable to more elaborate frailty tests, such as Fried Frailty Criteria or Short Physical Performance Battery, for predicting hospitalizations and mortality in cirrhosis [11]. Overall, the prevalence of pre-frailty (CFS > 3, 11 %) and frailty (CFS > 4, 4 %) were comparably low in our study, but comparable to a study in Canadian patients by Tandon et al. or a North American based multicenter study by Bajaj et al. [11,16]. This low prevalence may be best explained by the composition of our cohort, which only included out- or electively hospitalized patients and a high frequency of patients

with Child-Pugh A at study inclusion. That is why we decided to dichotomize the CFS in some analyses according to the cut-off for pre-frailty (CFS > 3) to increase the robustness of our statistical analyses.

The association between frailty and decompensation events have been extensively studied in the past [12,17–19]. However, the association of frailty and HE is less well studied in detail. In our current study, we found a higher CFS to be independently associated with the presence of CHE according to PHES. Moreover, a higher CFS was also associated with poorer results in S-ANT1, a test of semantic fluency and memory. Our study and studies by other groups demonstrate that there seems to be a bidirectional relationship between cognitive impairment and the presence of frailty [20,21]. However, it has to be acknowledged that due to the cross-sectional setting, we cannot delineate what comes first: frailty leading to a higher risk of CHE or vice versa. This has to be analyzed in future longitudinal studies.

Another important finding of our study was the strong association between a higher CFS or pre-frailty and the development of OHE during follow-up. These findings were robust even in sensitivity analyses including only patients without a history of OHE or when analyzing the endpoint of OHE and liver transplantation free survival. In this context, it is noteworthy that the association between CFS and OHE was independent of CHE at baseline. There is only one study available that is comparable to ours and investigated the predictive ability of CFS regarding OHE development. In a large study including 355 patients with cirrhosis, Ney et al. were able to demonstrate a robust association between CFS and OHE during follow-up and developed the easily applicable Montreal Cognitive Assessment (MoCA)-CFS score [22]. Our study expands the findings of the study by Ney et al., by providing data in a large cohort of European patients and demonstrating the predictive ability of CFS irrespective of CHE at baseline, which was not tested for in their study. A study by Tapper et al. investigated predictors for a first episode of OHE and found chair stands and daily activity—both potential measures of frailty—to be independently associated with a first episode of OHE [3]. Surprisingly, in this comprehensive study, performance in ICT, a validated test for detection of CHE, was not. Another recently published study demonstrated in a large North American based multicenter cohort that frailty - defined by CFS - and MHE were associated with hospital admissions [16]. Taken together, the aforementioned and our study underscore the usefulness of easily applicable tools for the detection of frailty, such as the CFS, to identify and monitor patients at higher risk for OHE. Especially CFS can be implemented into every outpatient clinic without any additional costs. Future studies should now focus on whether patients with e.g. a CFS > 3 would benefit from a prescription of a primary prophylaxis to prevent OHE. Currently,

no clear recommendation on this is possible, given the low quality of evidence of studies on this topic.

Frailty is a complex syndrome not only defined by sarcopenia and loss of muscle function, but also by cognitive dysfunctions. Sarcopenia has been studied extensively in the context of HE and the important role of muscle in ammonia metabolism is well described [23,24]. Recent studies demonstrated that aging processes make the brain more susceptible to toxic metabolites and consequently increasing the risk for HE [25,26]. Our study expands the current evidence on why frailty is associated with CHE as well as OHE by demonstrating in a well-matched cohort that patients with a CFS > 3 do suffer from higher levels of systemic inflammation and ammonia, independent of their underlying liver function. This is of pivotal importance given that ammonia and systemic inflammation are not only prerequisites for HE development, but also decompensation and mortality [27–29].

Our study has several strengths, such as the large and prospectively collected cohort, with thorough cognitive testing at baseline. However, there are also limitations that have to be acknowledged. First, this is a single center study conducted at a high-volume tertiary care center in Germany. Therefore, our findings may not be generalizable to every patient with cirrhosis. Second, we did not assess the presence of large portosystemic shunts, which are associated with the development of HE [30]. This is especially a limitation for our matched cohort looking at IL-6 and ammonia, because we cannot assure that the presence of portosystemic shunts is balanced between both groups. Third, we did not assess changes of CFS over time and are therefore unable to investigate the impact of relevant changes on the development of OHE. Fourth, we did not compare the predictive usefulness of CFS with sarcopenia. This is explained by the fact that only a minority of our (out-)patients has an available CT scan. This also underscores the limitation of sarcopenia determination using CT scans, as in most cases they are not available in every patient, whereas in CFS this is the case.

In conclusion, we were able to demonstrate that poorer physical functioning, quantified by CFS, is associated with the presence of CHE in patients without a history of OHE. Moreover, we found that a higher CFS is strongly associated with OHE development irrespective of the presence of CHE at baseline. As demonstrated in a matched subcohort, the higher frequency of HE in patients with a higher CFS may be explained by elevated levels of ammonia and systemic inflammation in frailer patients. CFS may serve as an easy and inexpensive tool to identify patients at higher risk of HE in clinical routine.

Data availability

Raw data are available from the corresponding author (C.L.) on reasonable request.

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Ethical statement

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (Nr. 837.232.17 [11066]). Written informed consent was obtained from all participants.

Conflict of interest

Leonard Kaps reports travel support from Gilead Sciences. Jörn M. Schattenberg reports consultancy to BMS, Boehringer Ingel-

heim, Echosens, Genfit, Gilead Sciences, Intercept Pharmaceuticals, Madrigal, Nordic Bioscience, Novartis, Pfizer, Roche, Sanofi, Siemens Healthcare GmbH and research funding from Gilead Sciences, Boehringer Ingelheim, and Siemens Healthcare GmbH, all unrelated to this research. Simon Gairing reports receiving travel and accommodation expenses from Ipsen. Christian Labenz reports travel expenses and consulting honoraria from Norgine and Merz Pharmaceuticals, lecture fee from Norgine, Intercept Pharmaceuticals/Advanz Pharma, Gilead Sciences and Merz Pharmaceuticals, and research grants from Norgine and Merz Pharmaceuticals, all unrelated to this research. The other authors disclose no potential financial or non-financial conflict of interests regarding this study.

Author contribution

Eva Maria Schleicher: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Validation, Visualization, Writing – original draft. **Leonard Kaps:** Investigation, Writing – review & editing. **Jörn M. Schattenberg:** Investigation, Writing – review & editing. **Peter Robert Galle:** Investigation, Resources, Software, Writing – review & editing. **Marcus-Alexander Wörns:** Investigation, Writing – review & editing. **Simon Johannes Gairing:** Conceptualization, Software, Writing – review & editing. **Christian Labenz:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.dld.2023.12.001](https://doi.org/10.1016/j.dld.2023.12.001).

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