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Applying Administrative Data-based Coding Algorithms for Frailty in Patients with Cirrhosis

Short Title: Claims-based Frailty Algorithms in Cirrhosis

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Abbreviations:

ADL, Activities of Daily Living

AUC, Area Under the ROC Curve

AUROC, Area Under Receiver Operating Characteristics curve

CCI, Charlson comorbidity index

CFI, Claims-based Frailty Index

CI, Confidence Interval

FFI, Fried Frailty Index

HCV, Hepatitis C Virus

HFRS, Hospital Frailty Risk Score

HE, Hepatic Encephalopathy

HRQOL, Health-Related Quality of Life

ICD, International Classification of Diseases

IQR, Interquartile Range

MELD-Na, Model for End-stage Liver Disease Sodium

NAFLD, Non-Alcoholic Fatty Liver Disease

NCT-A, Number Connection Test A

NCT-B, Number Connection Test B

SD, Standard Deviation

SHR, Subdistribution Hazard Ratio

SF-8, Short Form 8

SF-36, Short Form 36

SRT, Simple Reaction Time

PSQI, Pittsburgh Sleep Quality Index

Summary

Background: Frailty is a powerful prognostic tool in cirrhosis. Claims-based frailty scores estimate the presence of frailty without the need for in-person evaluation. These algorithms have not been validated in cirrhosis. Whether they measure true frailty or perform as well as frailty in outcome prediction is unknown.

Methods: We evaluated two claims-based frailty scores - Hospital Frailty Risk Score (HFRS) and Claims-based Frailty Index (CFI) - in 3 prospective cohorts comprising 1,100 patients with cirrhosis. We assessed differences in neuromuscular/neurocognitive capabilities in those classified as frail or non-frail based on each score. We assessed their ability to discriminate frailty based on the Fried Frailty Index (FFI), chair-stands, activities of daily living (ADL), and falls. Finally, we compared the performance of claims-based frailty measures and physical frailty measures to predict transplant-free survival using competing risk regression, and patient-reported outcomes.

Results: CFI identified neuromuscular deficits (balance, chair-stands, hip strength) while HFRS only identified poor chair-stand performance. CFI had an AUROC for identifying frailty as measured by FFI, ADLs, and falls of 0.57, 0.60, and 0.68, respectively; similarly, the AUROC

were 0.66, 0.63, and 0.67, respectively for HFRS. Claims-based frailty scores were associated with poor quality of life and sleep but were outperformed by the FFI and chair-stands. HFRS, per 10-point increase, (but not CFI) predicted survival of patients in the liver transplantation (SHR 1.08, 95%CI 1.03-1.12) and non-liver transplantation cohorts (SHR 1.13, 95%CI 1.05-1.22).

Conclusions: Claims-based frailty scores do not adequately associate with physical frailty but are associated with important cirrhosis-related outcomes.

Introduction

Frailty is an emerging indicator of poor outcomes in cirrhosis and liver transplantation.(1–4) It is a multidimensional construct informed by physical, cognitive, and psychosocial factors, which together quantify physiologic reserve. While many non-physical factors influence the development of frailty in cirrhosis,(1,5,6) the most validated frailty tools – Fried Frailty Index (FFI) and Liver Frailty Index(3,4) – include multiple physical performance measures such as hand-grip, chair-stands, and walk-speed.(7) These require in-person evaluation, effort, and time. As such, there is mounting interest in diagnosis code-based algorithms that could leverage administrative data in place of physical measurements.(8) The two most studied candidate algorithms (claims-based frailty index, CFI, and hospital frailty risk score, HFRS) have been developed from community dwelling elders >70 years old.(9,10) If validated in persons with cirrhosis, these algorithms will enable research on frailty at the population level.

Two crucial steps are required to validate frailty algorithms in cirrhosis. First, we must understand what frailty algorithms measure. To be considered a *frailty* index, they must discriminate deficits in the neuromuscular or neurocognitive capacities underlying frailty in cirrhosis. Second, as *frailty* predicts clinical outcomes, so too must the algorithms. In cirrhosis, frailty is linked to survival, liver transplant outcomes, and health-related quality of life (HRQOL).

Herein, we evaluated frailty algorithms using three separate cohorts of patients with cirrhosis with 3 aims. First, we evaluated whether the algorithms capture neuromuscular and neurocognitive deficits. Second, we assessed the test characteristics of each algorithm to discern

gold-standard frailty and disability measures. Third, we compared the performance of each algorithm with in-person measures of frailty for the prediction of mortality and poor HRQOL.

Materials and Methods

We conducted our study using three previously published prospective cohorts of patients with a confirmed diagnosis of cirrhosis from the University of Michigan Hepatology and Liver Transplant Clinics. The first cohort (cohort 1), conducted from August 2018 to April 2019, was used to define the differences in neuromuscular capacities according to frailty algorithm classification. The second cohort (cohort 2), conducted from July 2009 to February 2015, was used to compare the performance of each claims-based frailty measure against the FFI, as well as to assess outcomes of HRQOL and transplant-free survival. The third cohort (cohort 3), enrolled from July 2016 to August 2018 and followed through February 2020 was used to define performance of frailty algorithms against the Katz scale of Activities of Daily Living (ADLs) and for the prediction of transplant-free survival. Details of each cohort are presented in the **Supplementary Methods** and a conceptual overview of how they were used in the current study is presented in **Figure 1**.

Frailty indices

The FFI is the most widely utilized frailty tool in patients with organ failure awaiting transplantation.(11) The FFI includes subjective reports of exhaustion, weight loss, and physical activity as well as objective measures of walk-speed and hand-grip.(12) We used FFI as the gold-standard for frailty.

Two frailty algorithms based on administrative billing codes were studied. The Claims-based Frailty Index (CFI) was developed and validated based on a multivariable regression model of 52 International Classification of Diseases-9, 16 Healthcare Common Procedure Coding System, and 25 Current Procedural Terminology codes to predict deficit accumulation-based frailty(9). The CFI is calculated based on the presence or absence of these codes in the preceding 12 months with robust, pre-frail, mildly frail, and moderate-to-severely frail defined by scores of <0.15, 0.15-0.24, 0.25-0.34, and ≥0.35, respectively.(13) For the purposes of the current study, frailty was defined as a CFI score of ≥ 0.35. For each patient, codes were included in the algorithm from the preceding 12 months from their date of evaluation.

The Hospital Frailty Risk Score (HFRS) was developed and validated based on a multivariable logistic regression model of ICD-10 codes found to be prevalent in hospitalized patients.(10) The score is calculated based on the presence or absence of 109 ICD-10 codes in the preceding 24 months with patients categorized as low, intermediate, and high risk based on HFRS of < 5, 5-15, and >15, respectively. In a cohort of patients age 75 years and older, the HFRS significantly predicted 30-day mortality, length of stay, and 30-day readmissions after a hospitalization.(10) In the current study, HFRS frailty was defined as scores above 15. For each patient, codes were included in the algorithm from the preceding 24 months from their date of evaluation.

Outcomes

Aim 1: We first compared the differences in neuromuscular and neurocognitive capacities for persons classified as frail or non-frail according to the CFI and HFRS indices. Details of the neuromuscular assessments are presented in the **Supplement.** In brief, we assessed frailty using 30-second chair-stand test, grip strength, unipedal stance time, and hip strength using the lateral plank test. To assess neurocognition we used the Number Connection Tests A and B (NCT-A and NCT-B) and the simple reaction time measured using the ReactStick.

Aim 2: We evaluated the test characteristics of each claims-based frailty algorithm, CFI and HFRS, against the FFI according to their receiver operating characteristics. We also evaluated test-characteristics of the CFI and HFRS for disability using the Katz ADL scale, chair-stands, and fall history. Any ADL dependency, falls in the preceding six months, or chair-stands less than the median for the cohort was considered frail.

Aim 3: We evaluated each frailty measure with respect to their ability to discriminate the clinical outcomes of transplant-free survival and HRQOL. The main analysis was conducted in cohort B, a longitudinal cohort of patients evaluated for liver transplant, whose HRQOL was assessed using SF-36. We repeated this analysis in cohort C, a cohort of patients with Child A or B cirrhosis who were enrolled in a study to determine the cumulative incidence of hepatic encephalopathy, whose HRQOL was assessed using the SF-8 (Short Form 8) and the Pittsburgh Sleep Quality Index (PSQI).

Data Analyses

Descriptive data are presented as number (percent) for categorical data and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous data. Means for continuous neuromuscular and neurocognitive data were compared using the Student's t-test. Test performance was assessed using sensitivity, specificity, negative predictive value, and positive predictive value. A CFI ≥0.25 and a HFRS ≥5 can also be considered as defining frailty,(10,13) therefore a sensitivity analysis was performed using these cutoff values (**Supplemental Table 1 and 2**). The area under the receiver operating characteristic curve (AUROC) was calculated using continuous values of the frailty predictor variables.

The ability of the frailty scores (FFI, CFI, and HFRS) to predict mortality on the transplant waiting list in cohort 2 was assessed using Fine and Gray competing risk regression, presented as subdistribution hazard ratios (SHR), with transplantation as a competing event.(14) A priori, we determined we would assess the relationship between each frailty measure controlled for MELD-Na, hepatic encephalopathy, ascites, and the Charlson comorbidity index (CCI). Survival in cohort 3 was also analyzed using competing risk regression with transplantation as a competing event. Here, frailty measures included the administrative frailty measures (CFI and HFRS) in addition to the physical frailty measures of ADL dependency and chair-stands. A priori, we determined we would control for the MELD-Na score, Child class, and CCI. These variables were selected given their clinical importance in predicting survival in chronic liver disease.

This study was approved by the University of Michigan Medical School Institutional Review Board. Statistical analysis was performed using RStudio. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Baseline characteristics for each study cohort are presented in **Table 1**. As cohort 2 included patients evaluated in the liver transplant clinic, they had a higher median MELD-Na score of 13 (IQR 10-18) and a higher prevalence of decompensating events (55% with ascites and 39% with a history of hepatic encephalopathy) at enrollment. The prevalence of ICD-10 scores in cohort 2 used in the calculation of the CFI and HFRS are presented in **Supplemental**

Table 3 and 4. The correlation between the HFRS and CFI was 0.59, 0.63, and 0.63 in cohorts 1, 2, and 3, respectively.

Physiological Measures:

We first evaluated the neuromuscular and neurocognitive capacities of patients identified as frail or not according to the CFI and HFRS in cohort 1 (**Table 2).** Those classified as not frail by the CFI were able to complete more chair stands (11.6 vs 8.2, p<0.001), and maintain a unipedal stance and lateral plank position longer (15.2 vs 9.7 seconds, p=0.002 and 21.7 vs 10.1, p<0.001, respectively). Only chair stands were significantly better in those considered to be not frail by the HFRS (13.2 vs 9.8, p=0.04). For neurocognitive performance (NCT-A, NCT-B, and Simple Reaction Time), only the NCT-B was significantly associated with HFRS frailty.

Claims-Based Frailty Measures and Physical Frailty:

We next determined the ability of the CFI and HFRS to correctly group patients into frail and non-frail based on physical frailty measures (**Table 3**). We also examined whether the CFI and HFRS would discriminate disability (ADLs) or a history of falls. The CFI had an AUCROC for identifying frailty as measured by FFI, ADL dependency, and falls of 0.57, 0.60, and 0.68, respectively. For the HFRS, the corresponding AUROC values were 0.66, 0.63, and 0.67 respectively. Overall, the HFRS tended to be a very sensitive and less specific test for identifying physical frailty, and this difference increased on sensitivity analysis (HFRS frail cutoff of ≥5).(**Supplemental Table 2**)

Frailty Measures and Survival and Liver Transplantation:

In cohort 2, we evaluated the ability of frailty measures to predict mortality or transplantation in patients evaluated for liver transplantation (**Table 4**). Median follow-up was 589 days (IQR 150-1430) during which 201 (29.3%) patients died and 150 (21.9%) patients received a liver transplant. For each one-point increase in the FFI, there was a 43% increase in mortality (SHR 1.43, 95%CI 1.29-1.59). This remained significant controlling (individually) for MELD-Na score, the presence of hepatic encephalopathy, the presence of ascites, or Charlson comorbidity index. Higher FFI was significantly associated with a decreased likelihood of transplantation when adjusted for MELD-Na (SHR 0.82, 95%CI 0.73-0.93). A higher HFRS was

associated with an increased risk of mortality (SHR 1.08, 95%CI 1.03-1.12) even after adjustment for other clinical factors but HFRS was not predictive of transplantation. The CFI predicted neither death nor transplantation in this cohort. The ability to discriminate one-year transplant-free survival was highest for the FFI (AUROC 0.68), then the HFRS (AUROC 0.61), and lastly the CFI (AUROC 0.51). Only the FFI increased the predictive ability of the MELD-Na score (AUROC from 0.76 to 0.79).

In cohort 3, 42 (14.2%) patients died and 12 (4.1%) underwent liver transplantation during a median follow-up of 980 days (IQR 791-1122). Due to the small number of patients who underwent liver transplantation, prediction of this outcome was not analyzed. Mortality was significantly predicted by ADL disability (SHR 3.39, 95%CI 1.60-7.19) and chair-stands (SHR 0.88, 95% CI 0.84-0.93). Mortality was also predicted by both the CFI (SHR 1.13, 95%CI 1.08-1.19) and the HFRS (SHR 1.13, 95%CI 1.05-1.22). Prediction of mortality using both physical and claims-based frailty measures remained significant after adjusting for clinical factors.

Frailty Measures and Quality of Life:

In cohort 2, a SF-36 score less than 50 was significantly associated with CFI (OR 1.05, 95%CI 1.03-1.07), HFRS (OR 1.27, 95%CI 1.19-1.36), and FFI (OR 2.62, 95%CI 2.23-3.10). The FFI had the best ability to discriminate between those with SF-36 less than or greater than 50 (AUROC 0.79) followed by the HFRS (AUROC 0.66), then the CFI (AUROC 0.63).

In cohort 3, poor HRQOL was determined based on poor sleep (PSQI > 5) and low SF-8 scores (SF-8 < 50) and was best predicted by chair-stands (AUROC 0.65 and 0.75, respectively), followed by the CFI and HFRS. To a lesser extent, the Charlson comorbidity index predicted SF-8 scores (AUROC 0.57) (**Table 5**).

Discussion

Among patients with cirrhosis, frailty is strongly associated with diminished transplant-free survival,(1) hospitalization(15), and post-transplant outcomes.(16) Although it reflects deficits in neuromuscular and neurocognitive capacities, the concept of frailty is operationalized as poor performance on specific physical tests. However, these tests are rarely performed in clinical practice. Claims-based algorithms for frailty can be applied to populations provided they

are validated to identify frailty and predict frailty-related outcomes. In this study, we sought to validate the use of two claims-based frailty algorithms, the HFRS and CFI, for use in patients with cirrhosis. Both algorithms were associated with survival and poor HRQOL, albeit to a lesser degree than conventional physical frailty measures. Neither algorithm offered good discrimination or positive predictive values for physical frailty. However, the HFRS offered excellent sensitivity (and negative predictive values) for disability.

Frailty and Outcomes in Chronic Liver Disease

Physical frailty is known to predict mortality and poor HRQOL independent of MELD.(1–4,17) The value of claims-based frailty indices should be defined in part by their ability to reproduce similar associations. We found that claims-based frailty indices predicted mortality even after adjusting for MELD and cirrhotic decompensations.(**Table 3)** However, the FFI was better able to discriminate one-year transplant-free survival compared to the CFI and HFRS. Furthermore, only the addition of FFI improved MELD score prediction of transplant-free survival. Both the CFI and HFRS were associated with poor HRQOL and poor sleep but performed less well relative to physical measures such as FFI and chair-stands.

In the cohort of patients evaluated in the liver transplantation clinic, transplantation was not predicted by the claims-based scores or the FFI (except when adjusted for MELD). While frailty is associated with mortality on the liver transplant waiting list, it is but one of many factors weighted in transplantation decision-making.

Claims-Based Measures Poorly Discriminate Frailty

Identifying frailty in persons with cirrhosis is essential in order to subsequently implement targeted frailty-modifying interventions (nutritional, prehabilitation) that may improve outcomes.(3) Though CFI was associated with worsened neuromuscular performance, we found that both claims-based indices (CFI and HFRS) failed to adequately discriminate physical frailty. Our findings are consistent with those of the HFRS derivation cohort where there was poor agreement (kappa 0.30 and 0.22) between the HFRS with the Rockwood and FFI measures of frailty.(10) Compared to prior studies using the CFI, we found a lower discrimination ability of the CFI for FFI (AUROC 0.57 for our data vs 0.78 for others), but similar values in predicting ADL dependency (AUROC 0.70 for our data vs 0.66 for

others).(13,18) An important difference between the cohorts used to derive the claims-based frailty indices and our cohort is the markedly higher proportion of patients in our cohort classified as frail using administrative data. In prior studies, those identified as frail based on the CFI (≥ 0.35) or the HFRS (>15) comprised 2.2% and 20.0%, respectively.(10,13) Using these cutoffs, 10.2-46.2% (based on CFI) and 60.7-89.9% (based on HFRS) of patients in the current study were categorized as frail.

The CFI and HFRS are likely expanded measures of comorbidity

Our data show that claims-based frailty indices derived from the general population cannot be generalized to patients with cirrhosis. The reason that the algorithms cannot discriminate frailty in cirrhosis is because of the diagnostic codes that compose these scores.**(Supplemental Table 1)** For example, abnormal results of function studies (R94), other disorders of kidney and ureter (N28), unspecified renal failure (N19), and other disorders of fluid, electrolyte, and acid-base balance (E87) were found in more than half of cohort 2 (55% with ascites). Combined, these codes would classify a patient as at least intermediate risk frail based on the HFRS. These factors may identify frailty in the general population but are so common among patients with cirrhosis they are not discriminatory. This renders the claims-based frailty indices overly sensitive and non-specific among patients with cirrhosis. Beyond that, established contributors to the frail state in cirrhosis are missing from claims-based frailty indices. These conditions include sarcopenia, malnutrition, decompensating events, and hepatic dysfunction.(3,16,19)

In sum, the claims-based frailty algorithms appear to serve as a weighted comorbidity count that outperforms conventional comorbidity indices such as the Charlson comorbidity index.(20) We found that the CFI and HFRS are both associated with clinical and patient reported outcomes to a greater extent than the CCI. Kochar et al. showed patients with inflammatory bowel disease categorized as frail using an adapted HFRS had a median Charlson index of 6 compared to 2 in those not categorized as frail.(8)

The way forward for claims-based indices

Whether or not these algorithms track with frailty or comorbidity, they are associated with survival and patient-reported outcomes. As such, there is value in developing and refining

these resources for the cirrhosis population. Inputs into a potential algorithm should include appropriately weighted codes known to contribute to the frailty phenotype in cirrhosis, and these algorithms should predict frailty (and respond to frailty-modifying interventions) in cirrhosis. This will be challenging for two reasons. First, in a large retrospective study using natural language processing and ICD-codes to identify sarcopenia, frailty, and cachexia, 86% of patients with these conditions did not have the associated ICD-10 code and were identified only by natural language processing.(21) Even codes for HE or ascites are insensitive.(22,23) The major limitation of claims-based frailty indices is its dependence on a provider's recognition of the frail state with subsequent accurate coding. This adds both measurement error and subjectivity into the assessment of frailty. This runs counter to the trend of using more objective and standardized measures of frailty (e.g. Liver Frailty Index).(3,16)

Second, changes in frailty over time have important implications on cirrhosis-related outcomes.(24) The CFI and HFRS, however, are calculated from one to two years of prior data, respectively. This renders these scores relatively static and less likely to be meaningful in assessing the trajectory of the frail phenotype.

Finally, there remains value in the direct in-person assessment of frailty that cannot be accounted for in the use of administrative data. Involvement of the patient in the frailty evaluation allows for their direct observation and understanding of their current physical condition.

Contextual Factors

Our data must be interpreted in the context of the study design. First, we assessed the ability of physical and claims-based frailty measures to predict long-term survival. While the CFI has been validated to predict one- and two-year mortality(9,13), the HFRS was developed and externally validated to predict short-term (30-day) mortality.(10,25) Second, the CFI uses ICD-9 codes whereas the HFRS uses ICD-10 codes. In the current study, ICD-9 codes were mapped to their corresponding ICD-10 codes. Third, the cohorts were different in regard to their stage of liver disease; however, this was an advantage that allowed for the assessment of the claims-based algorithms in distinct populations. Fourth, frailty is a construct with multiple accepted tools and surveys used to diagnose its presence. Our selection of a subset of frailty tools to which to compare the performance of the claims-based indices introduced bias, but these are generally

accepted measures (or components) of frailty in cirrhosis.(3) Lastly, as discussed above, traditional cutoffs for each claims-based frailty measure applied to our cohorts resulted in a high proportion being classified as frail. We did not attempt to derive new cutoffs. Rather, we assessed major outcomes using the continuous values of these scores to better evaluate their ability to rank the outcomes of interest.

Conclusion

Claims-based data is useful tool for the evaluation of outcomes at the population level and have been used to develop indices for frailty. For patients with cirrhosis, the CFI and HFRS claims-based indices did not adequately discriminate physical frailty. Instead, they likely function as comorbidity indices. These tools are associated with mortality and patient reported outcomes, but to a substantially lower degree than gold-standard measures of frailty or disability. Future attempts to identify frailty in cirrhosis for population-based studies using claims-based indices would benefit from a derivation cohort composed of persons with cirrhosis.

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Figure 1: Description of the Three Cohorts of Patients Included in This Study and Specific Aims Each Cohort Was Used to Address

FFI, Fried Frailty Index; ADLs, Activities of Daily Living; NCT-A, Number Connection Test A; NCT-B, Number Connection Test B; SRT, Simple Reaction Time

Table 1: Demographics and Clinical Characteristics of the Cohorts

	Cohort 1 Cirrhosis patients evaluated for neurocognitive and muscular capacities N=119	Cohort 2 Longitudinal cohort of cirrhosis patients referred for liver transplant evaluation N=685	Cohort 3 Longitudinal cohort of cirrhosis patients without hepatic encephalopathy at enrollment N=296
Age, years	62 (58-68)	56 (49-61)	60 (52-66)
Sex, female	59 (49.6%)	270 (39%)	128 (43%)
Nonwhite	6 (5%)	96 (14.0%)	-
Body Mass Index, kg/m^2	30.7 (26.3-35.7)	28.6 (24.4-33.6)	29.3 (25.7-34.0)
Etiology of Cirrhosis:			
NAFLD	41 (34%)	157 (23%)	97 (33%)
Alcohol	28 (24%)	166 (24%)	65 (22%)
HCV	18 15%)	156 (23%)	89 (30%)
other	32 (27%)	206 (30%)	45 (15%)
Charlson Comorbidity Index	-	2 (1-3)	4 (1-4)
Child class A/B/C	95/21/2*	-	207/89/0
Ascites	-	374 (55%)	120 (41%)
HE	-	268 (39%)	0
MELD-Na	9 (8-13)	13 (10-18)	9 (7-13)
Albumin (g/dL)	-	3.2 (IQR 2.7-3.7)	4.0 (3.6-4.3)
CFI	0.348 (0.315-0.377)	0.16 (0.109-0.276)	0.338 (0.287-0.371)
Robust	2.5%	47.9%	2.0%
Prefrail	7.6%	23.4%	14.5%
Mildly frail	43.7%	18.5%	43.9%
Moderate-to-severely frail	46.2%	10.2%	39.5%
HFRS	45.90 (26.20-81.30)	20.20 (6.30-45.90)	39.3 (21.5-66.8)
Low risk	3.4%	21.2%	2.4%
Intermediate risk	6.7%	18.1%	13.9%
High risk	89.9%	60.7%	83.8%

Values presented as median (IQR, Interquartile Range) or number (percent)

NAFLD, Non-Alcoholic Fatty Liver Disease; HCV, Hepatitis C Virus; HE, Hepatic Encephalopathy; MELD-Na, Model for End-stage Liver Disease Sodium; CFI, Claims-based Frailty Index; HFRS, Hospital Frailty Risk Score

*****1 patient had unknown Child class, - Race not collected

Table 2: Neurocognitive and Muscular Capacities in Cohort 1 Patients with and without Frailty based on CFI and HFRS

	Cirrhosis patients evaluated for neurocognitive and muscular capacities (Cohort 1)					
	CFI			HFRS		
Mean value	Not Frail N=64	Frail N=55	p-value	Not Frail N=12	Frail N=107	p-value
Unipedal stance (sec)	15.2	9.7	0.002	18.3	12.0	0.09
Chair Stands in 30 seconds	11.6	8.2	<0.001	13.2	9.8	0.04
Hand grip (avg of 6 in lbs)	55.6	49.8	0.2	56.7	52.4	0.63
Lateral plank test (sec)	21.7	10.1	<0.001	19.9	15.7	0.47
Melbourne visual contrast (db)	22.1	21.2	0.22	22.8	21.7	0.04
Vibratory sense (sec)	10.7	8.0	0.01	13.7	9.0	0.007
Neurocognitive						
NCT-A (sec)	37.8	43.5	0.07	33.8	41.1	0.09
NCT-B (sec)	96.2	112.6	0.07	82.4	105.9	0.04
Simple Reaction Time (ms)	232.4	219.2	0.13	236.3	225.1	0.50

CFI, Claims-based Frailty Index; HFRS, Hospital Frailty Risk Score; SD, Standard Deviation; NCT-A, Number Connection Test A; NCT-B, Number Connection Test B. For both frailty risk scores, we used the cutoff for 'severe' frailty: CFI ≥ 0.35 or HFRS > 15

Table 3: Test Performance of Claims-Based Frailty Measures and Physical Frailty Measures in Cohorts 2 and 3

		Cohort 2 Longitudinal cohort of cirrhosis patients referred for liver transplant evaluation	Cohort 3 Longitudinal cohort of cirrhosis patients without hepatic encephalopathy at enrollment		
		Frailty Outcomes			
		Frail FFI performance	Dependent for performance of ADLS	Frail Chair-Stand performance	Falls within 6 months
Claims-based Frailty Index (CFI)	Sens	0.13	0.65	0.54	0.62
	Spec	0.92	0.63	0.72	0.67
	NPV	0.60	0.95	0.67	0.87
	PPV	0.51	0.15	0.60	0.33
	AUC	0.57	0.70	0.62	0.68
Hospital Frailty Risk Score (HFRS)	Sens	0.73	0.96	0.88	0.95
	Spec	0.48	0.17	0.46	0.19
	NPV	0.72	0.98	0.67	0.94
	PPV	0.49	0.10	0.46	0.24
	AUC	0.66	0.63	0.63	0.67

FFI, Fried Frailty Index; ADL, Activities of Daily Living; NPV, Negative Predictive Value; PPV, Positive Predictive Value; AUC, Area Under the Curve

Physical frailty was defined as a FFI ≥3, any ADL dependency, Chair-stands below the median (< 10), and any Falls within the preceding 6 months. Claims-based frailty was defined as a CFI ≥ 0.35 or HFRS > 15. AUC performed using continuous values of the CFI and HFRS.

Table 4: Association between Frailty Measures or Algorithms and Mortality using Competing Risk Regression in Cohorts 2 and 3

		Cohort 2 Longitudinal cohort of cirrhosis patients referred for liver transplant evaluation		Cohort 3 Longitudinal cohort of cirrhosis patients without hepatic encephalopathy at enrollment	
		Death	Transplant		Death
		SHR (95% CI)	SHR (95% CI)		SHR (95% CI)
	CFI (per 0.01-point increase)	1.00 (0.99-1.02)	0.99 (0.97-1.01)	CFI (per 0.01-point increase)	**1.13 (1.08-1.19)**
Adjusted models	+ MELD-Na	1.00 (0.99-1.02)	0.99 (0.97-1.00)	+ MELD-Na	**1.13 (1.07-1.19)**
	+ HE	1.00 (0.99-1.02)	0.99 (0.97-1.01)	+ CTP-B	**1.14 (1.08-1.20)**
	+ Ascites	1.01 (0.99-1.02)	0.99 (0.97-1.00)	+ CCI	**1.13 (1.07-1.19)**
	+ CCI	1.00 (0.99-1.02)	0.99 (0.97-1.01)		
	HFRS (per 10-point increase)	**1.08 (1.03-1.12)**	1.04 (0.98-1.10)	HFRS (per 10-point increase)	**1.13 (1.05-1.22)**
Adjusted models	+MELD-Na	**1.05 (1.00-1.10)**	1.00 (0.93-1.06)	+ MELD-Na	**1.11 (1.03-1.20)**
	+HE	**1.07 (1.03-1.12)**	1.04 (0.98-1.10)	+ CTP-B	**1.14 (1.06-1.23)**
	+Ascites	**1.08 (1.04-1.13)**	1.04 (0.98-1.09)	+ CCI	**1.11 (1.03-1.20)**
	+ CCI	**1.07 (1.03-1.12)**	1.05 (0.99-1.10)		
	FFI (per 1-point increase)	**1.43 (1.29-1.59)**	0.91 (0.81-1.02)	ADL – any disability	**3.39 (1.60-7.19)**
Adjusted models	+ MELD-Na	**1.37 (1.22-1.53)**	**0.82 (0.73-0.93)**	+ MELD-Na	**3.59 (1.67-7.72)**
	+ HE	**1.41 (1.27-1.57)**	0.90 (0.81-1.01)	+ CTP-B	**3.46 (1.64-7.31)**
	+ Ascites	**1.40 (1.26-1.57)**	0.92 (0.82-1.04)	+ CCI	**3.41 (1.61-7.20)**
	+ CCI	**1.41 (1.27-1.57)**	0.92 (0.82-1.03)		
Adjusted models				Chair Stands (per 1-point increase)*	**0.88 (0.84-0.93)**
				+ MELD-Na	**0.89 (0.84-0.94)**
				+ CTP-B	**0.89 (0.84-0.94)**
				+ CCI	**0.89 (0.84-0.94)**

*Increasing number of chair stands reflects a robust state. Bolded values which were statistically significant.

We used Fine-Gray competing-risk regression to test the association between each frailty metric and the outcome of death or transplantation for our two cohorts with longitudinal data. The univariable subdistribution hazard distribution ratios (SHR) are presented for each frailty metric and then adjusted by sequentially adding other factors (bivariable analysis). In cohort 2, we adjusted for MELD-Na, HE, ascites, and Charlson Comorbidity Index (CCI); In cohort 3, we added MELD-Na followed by Child class B and CCI.

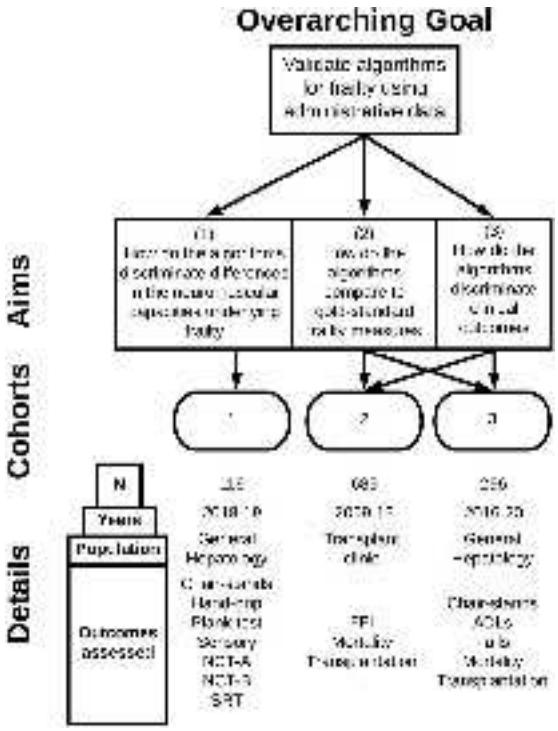
CFI, Claims-based Frailty Index; CI, Confidence Interval; MELD-Na, Model for End-stage Liver Disease Sodium; HE, Hepatic Encephalopathy; CTP-B, Child Turcotte Pugh B; HFRS, Hospital Frailty Risk Score; FFI, Fried Frailty Index; ADL, Activities of Daily Living

Table 5: Association between Health-related Quality of Life and Frailty Measures or Algorithms

		Cohort 2 Referred for liver transplant evaluation	Cohort 3 Longitudinal cohort without hepatic encephalopathy	
		Outcomes		
		Poor Health-Related Quality of Life (SF-36 <50)	Severe Sleep Impairment (PSQI)	Poor Health-Related Quality of Life (SF8 <50)
CFI (per 0.01-point increase)	OR (95% CI)	1.05 (1.03-1.07)	1.05 (1.02-1.09)	1.11 (1.06-1.18)
	AUC	0.63	0.61	0.69
HFRS (per 10-point increase)	OR (95% CI)	1.27 (1.19-1.36)	1.12 (1.04-1.22)	1.23 (1.13-1.34)
	AUC	0.66	0.59	0.72
Fried (per 1-point increase)	OR (95% CI)	2.62 (2.23-3.10)		
	AUC	0.79		
Chair-Stands (per 1-point increase)	OR (95% CI)		0.91 (0.86-0.95)	0.83 (0.78-0.89)
	AUC		0.65	0.75
CCI (per 1-point increase)	OR (95% CI)	1.28 (1.14-1.45)	1.01 (0.94-1.09)	1.10 (1.01-1.19)
	AUC	0.59	0.50	0.57

SF-36, Short Form 36; PSQI, Pittsburgh Sleep Quality Index; SF-8, Short Form 8; CFI, Claims-based Frailty Index; OR, Odds Ratio; CI, Confidence Interval; AUC, Area Under the Curve; HFRS, Hospital Frailty Risk Score; CCI, Charlson Comorbidity Index

We evaluated two measures of global health-related quality of life – the SF-36 and SF-8. Both are considered 'poor' when the score is <50. We also examined sleep quality using severe sleep impairment on PSQI as an outcome. Blacked out squares reflect a lack of such data for cohort.



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