Hospital frailty risk score is superior to legacy comorbidity indices for risk adjustment of in-hospital cirrhosis cases
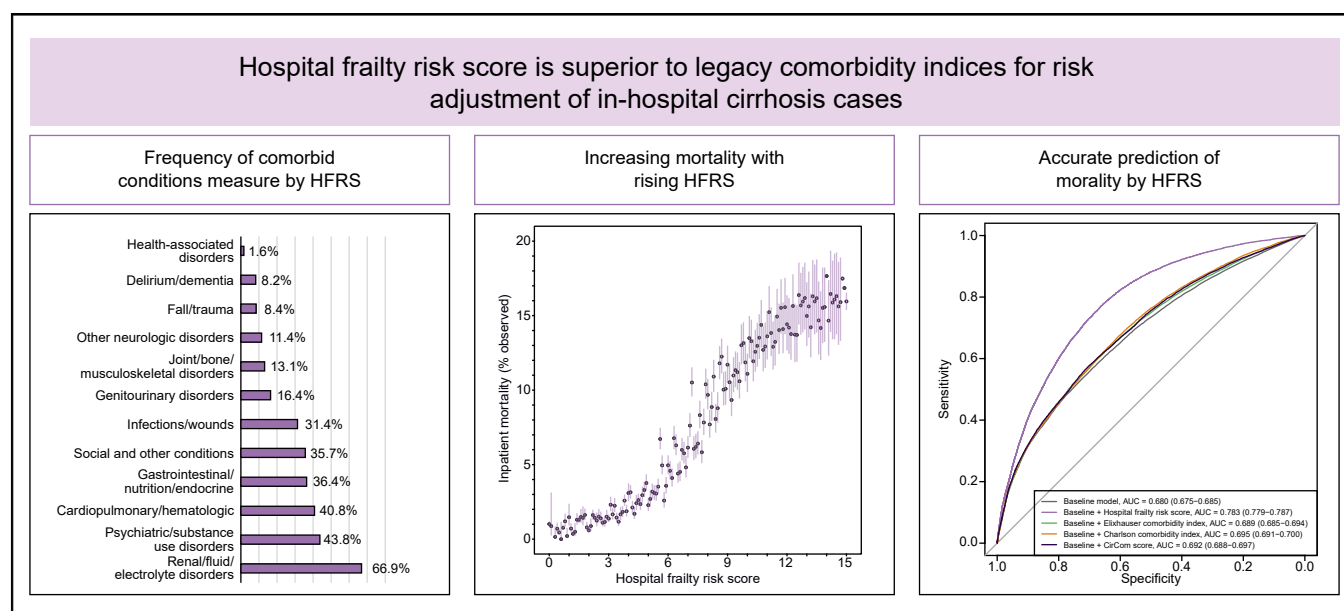
Authors

Archita P. Desai, Swetha Parvataneni, Shannon M. Knapp, Lauren D. Nephew, Naga Chalasani, Marwan S. Ghabril, Eric S. Orman

Correspondence

desaiar@iu.edu (A.P. Desai), esorman@iu.edu (E.S. Orman).

Graphical abstract

Hospital frailty risk score is superior to legacy comorbidity indices for risk adjustment of in-hospital cirrhosis cases

Highlights

- Using over 600,000 hospital discharge records of cirrhosis, we assessed the performance of risk adjustment tools.

- HFRS and legacy risk adjustment tools capture high rates of comorbidities and are associated with inpatient mortality.

- HFRS measures a larger variety of comorbid conditions and demonstrated significantly improved prediction of inpatient mortality *vs.* other tools.

- Within each level of the ECI, CCI, and CirCom, we noted significant variations in mortality that could be identified by the HFRS.

Impact and Implications

We compared commonly used comorbidity indices to a more recently described risk score (hospital frailty risk score [HFRS]) in patients with cirrhosis using a national sample of hospital records. Comorbid conditions are common in hospitalised patients with cirrhosis. There is significant variability in mortality across the range of each index. HFRS outperforms the Charlson comorbidity index, Elixhauser comorbidity index, and CirCom (cirrhosis-specific comorbidity scoring system) in predicting inpatient mortality. HFRS is a valuable index for risk adjustment in inpatient administrative database studies.

Hospital frailty risk score is superior to legacy comorbidity indices for risk adjustment of in-hospital cirrhosis cases

Archita P. Desai,[1,*] Swetha Parvataneni,[1] Shannon M. Knapp,[2] Lauren D. Nephew,[1,3] Naga Chalasani,[1,4]
Marwan S. Ghabril,[1] Eric S. Orman[1,*]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Division of Cardiovascular Medicine, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [3]Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN, USA; [4]Indiana University Health, Indianapolis, IN, USA

Background & Aims: The hospital frailty risk score (HFRS) identifies older patients at risk of poor outcomes and may have value in cirrhosis. We compared the Charlson (CCI), Elixhauser (ECI), and cirrhosis (CirCom) comorbidity indices with the HFRS in predicting outcomes for cirrhosis hospitalisations.
Methods: Using the National Inpatient Sample (quarter 4 of 2015–2019), we analysed cirrhosis hospitalisations. For each index, we described the prevalence of comorbid conditions and inpatient mortality. We compared the ability of CCI, ECI, CirCom, and HFRS to predict inpatient mortality. Raw and adjusted models predicting inpatient mortality were compared using the area under the receiver operating characteristic curve and the Akaike information criterion.
Results: The cohort's (N = 626,553) median age was 61 years (IQR 52–68 years), 60% were male, cirrhosis was caused by alcohol in 43%, and 38% had ascites. The median comorbidity scores are as follows: ECI 4 (IQR 3–6), CCI 5 (IQR 4–8), and HFRS 5.6 (IQR 3.0–8.6). The most common CirCom score was 0 + 0 (44%). Across the range of values of each index, we observed different mortality ranges: CCI 1.9–13.1%, ECI 3.2–8.7%, CirCom 4.9–13.8%, and HFRS 1.0–15.2%. An adjusted model with HFRS had the highest area under the receiver operating characteristic curve in predicting mortality (HFRS 0.782 *vs.* ECI 0.689, CCI 0.695, and CirCom 0.692). We observed substantial variation in mortality with HFRS within each level of CCI, ECI, and CirCom. For example, for ECI 4, mortality increased from 0.6 to 16.4%, as HFRS increased from 0 to 15.
Conclusions: Comorbidity indices predict inpatient cirrhosis mortality, but HFRS performs better than CCI, ECI, and CirCom. HFRS is an ideal tool for measuring comorbidity burden and disease severity risk adjustment in cirrhosis-related administrative database studies.
Impact and Implications: We compared commonly used comorbidity indices to a more recently described risk score (hospital frailty risk score [HFRS]) in patients with cirrhosis using a national sample of hospital records. Comorbid conditions are common in hospitalised patients with cirrhosis. There is significant variability in mortality across the range of each index. HFRS outperforms the Charlson comorbidity index, Elixhauser comorbidity index, and CirCom (cirrhosis-specific comorbidity scoring system) in predicting inpatient mortality. HFRS is a valuable index for risk adjustment in inpatient administrative database studies.

Introduction

With increasing availability of big data, a growing number of registries, clinical data warehouses, and administrative datasets are being used to study liver-related outcomes.[1–4] Collectively, these datasets are used for a variety of purposes including facilitating health services research and supporting health system goals. Regardless of their purpose, appropriate risk adjustment, often for comorbid conditions that can contribute to poor outcomes, is crucial to making valid comparisons between groups.[5,6] In liver disease, commonly used non-proprietary tools include the Elixhauser comorbidity index (ECI), the Charlson comorbidity index (CCI; Deyo modification), and CirCom, a cirrhosis-specific comorbidity scoring system.[7–9]

Although these are important tools, with time our understanding of conditions relevant to liver disease outcomes has changed. These changes then affect clinical documentation and diagnosis capture, which can in turn impact the performance of risk adjustment tools.[10,11] A notable example in geriatrics is the understanding that frailty-related diagnoses increase mortality risk.[12,13] This knowledge has also been adapted to liver disease, and it is now widely accepted that physical frailty is a key determinant of mortality in individuals with cirrhosis.[14,15] In line with this advancement, diagnosis code-based tools such as the claims-based frailty index and the hospital frailty risk score (HFRS) have been developed in the geriatric population to predict

ELSEVIER

EASL
The Home of Hepatology

mortality.[16,17] When adapted to liver disease, HFRS independently predicts mortality in those awaiting liver transplant.[18] Despite its name, HFRS measures more than just frailty and can identify other comorbid conditions in individuals with cirrhosis.[19–21]

Although increasing numbers of cirrhosis studies rely on large administrative datasets, traditional risk adjustment tools such as CCI, ECI, and CirCom have not been compared with newer tools such as HFRS. In this study, we compared the performance of three commonly used indices (CCI, ECI, and CirCom) with that of HFRS in a large, hospitalised cohort with cirrhosis. We aimed to (1) describe the prevalence of different comorbid conditions across these indices, (2) describe the variations in predicted and observed mortality with each index, and (3) compare the performance of each index in predicting mortality.

Patients and methods

Study design

Data were obtained from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) from quarter 4 of 2015 through 2019. It is the largest inpatient database in the USA and collects data from a sample of US hospitals from 46 states and the District of Columbia, covering 97% of the US population. Annually, the NIS captures data from approximately 7 million hospital stays, estimating more than 35 million hospitalisations. Each hospitalisation is de-identified and carries demographic and hospital characteristics as well as up to 40 diagnosis codes (2015–2016: 30 codes; 2017–2019: 40 codes) and 25 procedure codes (2015–2016: 15 codes; 2017–2019: 25 codes), which are extracted using standardised coding forms. Data quality is maintained by HCUP through independent external review of each data source annually.[22,23]

Inclusion and exclusion criteria

We included admissions for individuals aged ≥18 years if they contained at least one diagnosis code indicating cirrhosis in either the primary or secondary diagnoses. Diagnoses were extracted through the ICD-10 diagnosis codes as defined in Table S1.[24,25]

Variables of interest

Risk indices (CCI, ECI, CirCom, and HFRS) were calculated using ICD-10 codes (Table S1). Covariates extracted from the NIS databases include patient-level demographics (age, sex, race/ethnicity, and insurance) and clinical characteristics (aetiology of cirrhosis, and both the presence and absence of complications associated with cirrhosis) (Table S1).

Charlson comorbidity index
CCI was adapted for use in administrative datasets and includes 17 comorbidities that carry varying weights (Table 1).[8] Further modification to translate to the ICD-10 coding system was used for this study.[26] The CCI score ranges from 0 to 29. For this study, we capped the index at 15, as only 0.2% of all discharges had a CCI beyond this score.

Elixhauser comorbidity index
ECI was developed specifically for use in administrative data using ICD-9 diagnosis codes and later adapted for 1CD-10 diagnosis codes.[7,26] The index includes 30 comorbidities, each weighted equally (Table 1). We used previously described software specifically designed for use with the NIS dataset to

calculate the ECI score.[27] For this study, we excluded liver disease categories in ECI. In addition, we capped the score at 10, as only 0.18% of all discharges had an ECI beyond this score.

Cirrhosis comorbidity index
The CirCom score was developed for use specifically in individuals with cirrhosis.[9] The score includes nine comorbidities at three levels, with each comorbidity assigned a different weight (Table 1).[9] A CirCom score of 0 was assigned to those with no comorbidities identified, a score of x + x if comorbidities were identified at multiple levels, and 1 + 1 if the patient had two or more of the lower acuity comorbidities but none of the severe comorbidities. For example, if a patient had active metastatic cancer and one or more of the listed lower acuity comorbidities, they would be assigned 5 + 1. Similarly, if a patient had active metastatic cancer and did not have more than one of the listed primary comorbidities, the score was 5 + 0. Patients with no comorbidities except liver disease were assigned a CirCom score of 0. The highest CirCom score is 5 + 1.

Hospital frailty risk score
HFRS was developed to identify recently hospitalised elderly individuals (age >75 years) who are frail and are at high risk for adverse outcomes (hospitalisation and mortality) within administrative datasets.[16] The score is a sum of weights assigned to 109 ICD-10 codes when present in the medical record in the preceding 24 months and continuously ranges from 0 to 99 (Table 1). For this study, we calculated HFRS based on ICD-10 codes limited to the encounter of interest given the limitations of the NIS. We also grouped the ICD-10 codes into 12 subcategories: delirium/dementia, fall/trauma, neurologic disorders, fluid/electrolyte disorders, infection/wounds, social/other conditions, cardiorespiratory/haematologic, gastrointestinal/nutrition/endocrine, joint/bone health/musculoskeletal, genitourinary, healthcare associated, and psychiatric/substance abuse (Table S1). HFRS ranges from 0 to 99 but was capped at 15, as only 3% of all discharges had an HFRS beyond this score.

Outcomes

The primary outcome was inpatient mortality. For each index, we described the prevalence of comorbid conditions and the observed range in inpatient mortality. We then compared the accuracy of predicting inpatient mortality in separate models containing CCI, ECI, CirCom, or HFRS.

Statistical analysis

Cohort characteristics were summarised using percentages (categorial variables) and medians with IQRs (continuous variables). For observed mortality, CIs were calculated using Wilson's method in the R package 'binom'.[28,29] To model inpatient mortality, we opted to use generalised additive models (GAMs), as logistic regression resulted in a poor fit of predicted to observed mortality, particularly across the span of HFRS.[30] We found that GAMs provided a far better fit. GAMs were fit using the gam function in the R package 'mgcv' and used a logit link (as used in logistic regression).[30] The baseline model included sex, ascites, hepatic encephalopathy, variceal haemorrhage (covariates with odds ratio >1.2 in Table S2), and a smooth function of age, using thin plate regression splines for the smoothing function. We then modelled mortality in separate models, adding each of the indices to the baseline model. For CCI, ECI, and HFRS, the score was added as a smooth function

Table 1. Summary of comorbid indices studied.

Comorbidity indices	Comorbidities measured		Scoring
Charlson comorbidity index (score range: 0–29)	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Hemiplegia or paraplegia Renal disease Moderate–severe liver disease	Chronic pulmonary disease Rheumatic disease Peptic ulcer disease Mild liver disease Diabetes without chronic complication Diabetes with chronic complication Malignancy/leukaemia/lymphoma	1 point for any code/diagnosis in each category present 2 points for any code/diagnosis in each category present 3 points for any code/diagnosis in each category present
	Metastatic solid tumour	AIDS	6 points for any code/diagnosis in each category present
Elixhauser index (score range: 0–30)	Hypertension Fluid and electrolyte disorders Coagulopathy Deficiency anaemias Alcohol abuse Renal failure Chronic pulmonary disease Diabetes with chronic complications Congestive heart failure Obesity Depression Pulmonary circulation disease Lymphoma AIDS	Diabetes without chronic complications Weight loss Hypothyroidism Other neurological disorders Drug abuse Valvular disease Peripheral vascular disease Psychoses Solid tumour without metastasis Metastatic cancer Peptic ulcer disease with bleeding Rheumatoid arthritis/collagen vascular disease Chronic blood loss Paralysis	1 point for each code/diagnosis in each category
CirCom (score categories: 0, 1 + 0, 1 + 1, 3 + 0, 3 + 1, 5 + 0, and 5 + 1)	Active metastatic cancer Active myocardial infarction Active non-metastatic or haematologic cancer Chronic obstructive pulmonary disease Acute myocardial infarction Peripheral arterial disease Epilepsy	Inactive metastatic cancer Chronic kidney disease Substance abuse other than alcoholism Heart failure Non-metastatic or haematologic cancer	5 if any condition present 3 if any condition present 1 if any condition present
Hospital frailty risk score* (score range: 0–99)	Renal/fluid/electrolyte disorders Psychiatric/substance use disorders Cardiopulmonary/haematologic Gastrointestinal/nutrition/endocrine Social and other conditions Infections/wounds	Genitourinary disorders Joint/bone/musculoskeletal Disorders Other neurologic disorders Fall/trauma Delirium/dementia Healthcare-associated disorders	Unique weight applied to each ICD code

* Categories for the hospital frailty risk score were created for this paper.

using thin plate regression splines. Because of the nature of CirCom (*e.g.* 3 + 0 and 3 + 1 are not treated as numerically 3 and 4, respectively, and there are only seven possible values), it was added as a categorical variable. To build and evaluate these models, we randomly split the data into two sets, with 50% of the observations used as a training set (to build the models) and the remaining 50% as a validation set (to compare the models). Receiver operating characteristic curves and AUC, as well as Akaike information criterion and Bayesian information criterion, were calculated using only the validation set.

Results

Study population

A total of 626,553 discharges with cirrhosis were included for analysis. Table 2 describes the study population. The median age was 61 years (IQR 52–68 years), and 60% were men. Race and ethnicity were reported as White in 65%, 10% Black, 16% Hispanic, and 9% other. The most common cause of cirrhosis was alcohol

(43%), followed by non-alcoholic steatohepatitis (31%) and hepatitis C (22%). Complications of cirrhosis were common: 38% had ascites, 9% had hepatic encephalopathy, 5% had variceal haemorrhage, and 5% had hepatocellular carcinoma. The overall observed inpatient mortality rate was 5.8%. Table 3 summarises each comorbidity index score. The median (IQR) scores were as follows: ECI 4 (3–6), CCI 5 (4–8), and HFRS 5.6 (3.0–8.6). The most common category for CirCom was 0 (44%) followed by 1 + 0 (18.5%) and 3 + 1 (16.6%).

Prevalence of comorbid conditions within each comorbidity index

We examined the prevalence of component categories within each index (Fig. 1). Within ECI, the three most common categories were hypertension (58%), fluid and electrolyte disorders (51%), and coagulopathy (39%). Within CCI, renal disease (26%), chronic obstructive pulmonary disease (COPD) (25%), and congestive heart failure (CHF) (22%) were the most common comorbidities. In CirCom, chronic kidney disease (CKD) (25%),

Table 2. Study population characteristics.

Population characteristics	Total cohort (N = 626,553)
Demographics	
Age (years), median (IQR)	61 (52–68)
Male sex, n (%)	373,212 (59.6)
Race/ethnicity*, n (%)	
White	405,007 (64.6)
Black	63,881 (10.2)
Hispanic	101,497 (16.2)
Other	40,056 (6.4)
Insurance/payer†, n (%)	
Medicaid	153,695 (24.5)
Medicare	300,583 (48.0)
Private/HMO	117,621 (18.8)
Other	53,734 (8.6)
Cirrhosis characteristics	
Aetiology of cirrhosis, n (%)	
Hepatitis C	135,581 (21.6)
Alcohol	270,312 (43.1)
NASH	193,098 (30.8)
Other‡	32,297 (5.2)
Cirrhosis complication, n (%)	
Ascites	239,536 (38.2)
Hepatic encephalopathy	57,872 (9.2)
Variceal haemorrhage	31,914 (5.1)
Hepatocellular carcinoma	30,842 (4.9)
Hospital outcome	
Cost of admission (2019 US$), median (IQR)	10,102 (6,036–18,262)
Length of stay (days), median (IQR)	4 (2–7)
Inpatient mortality, n (%)	36,210 (5.8)

* Missing in 16,112 (2.6%); 'Other' includes Asian, American Indian, and Alaska Native.
† Missing in 920 (0.2%); 'Other' includes self-pay and no charge.
‡ 'Other' includes unspecified viral hepatitis, cryptogenic hepatitis, Wilson disease, hereditary haemochromatosis, alpha-1 antitrypsin deficiency, primary biliary cirrhosis, secondary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis. HMO, health maintenance organisation; NASH, non-alcoholic steatohepatitis.

CHF (21%), and COPD (20%) were the most common. In HFRS, the most common were renal, fluid, and electrolyte disorders (67%); psychiatric and substance use disorders (44%); and cardiopulmonary and haematologic disorders (41%).

Observed inpatient mortality and comorbidity index scores

Compared with those who survived the hospitalisation, those who died had higher scores for each of the indices (Table 3). For each index, we also observed a large range in mortality (Fig. 2). For ECI, the mortality ranged from 3.2% for ECI 0 (95% CI 2.9–3.6%) to 8.7% for ECI 10 (95% CI 8.7–9.6%). For CCI, mortality

ranged from 1.9% for CCI 1 (95% CI 1.8–2.1%) to 13.1% for CCI 15 (95% CI 11.8–14.4%). In both ECI and CCI, the increase in mortality appeared linear. With CirCom, inpatient mortality was relatively stable near 5% for the first three categories (0, 0 + 1, and 1 + 1) and then increased substantially to 13.8% for CirCom 5 + 1 (95% CI 13.1–14.5%). For HFRS, we noted the largest range in mortality with 1.0% for HFRS 0 (95% CI 0.9–1.2%) up to 16.4% for HFRS 14.0 (95% CI 14.7–15.7%). As with ECI and CCI, mortality also increased as HFRS increased; however, we observed an 'S'-shaped relationship with relatively smaller changes in mortality at the two extremes of HFRS scores (Fig. 2D). Table S2 compares relevant admissions characteristics of those who survived *vs.* died during the hospitalisation. Notably, within these characteristics, liver disease complications had the highest odds ratio for inpatient mortality.

Performance of comorbidity index in predicting mortality

Next, we compared the performance of each index in predicting inpatient mortality using receiver operating characteristic curves and AUC in the validation dataset (Fig. 3). In unadjusted models, HFRS showed the strongest performance with AUC of 0.746 (95% CI 0.743–0.750). In models adjusted for age, sex, ascites, hepatic encephalopathy, and variceal haemorrhage, HFRS showed the strong performance with AUC of 0.782 (95% CI 0.778–0.785; adjusted model) as well as the lowest Akaike information criterion and Bayesian information criterion (Fig. 3 and Table S3). ECI, CCI, and CirCom had lower AUCs with CirCom having the lowest AUC (marginally) of 0.692 (95% CI 0.688–0.696).

Distribution of HFRS across other comorbidity index scores

Because HFRS had a superior performance in predicting inpatient mortality and incorporates more conditions than the other scores, we evaluated the distribution of HFRS across the spectrum of the other indices. In addition, we assessed the relationship between observed mortality and different combinations of HFRS and ECI, CCI, or CirCom scores using heat maps (Fig. 4). We noted greater variation in observed mortality (represented by the range of colours) across the y-axis (representing the range of HFRSs) than across the x-axis (representing the range of ECI, CCI, or CirCom scores). For example, at the y-axis value of 5.6 (median HFRS in the cohort), mortality across ECI scores (x-axis) ranged from 8.3 to 16.0% (from green to blue range of colours). In comparison, at the x-axis value of 4 (median ECI in the cohort), mortality across HFRSs (y-axis) ranged from 0.6 to 16.4% (from

Table 3. Summary of comorbidity index scores in study population by outcome of the hospitalisation.

Comorbidity indices	Total cohort (N = 626,553)	Alive (n = 590,343)	Died (n = 36,210)
Elixhauser index, median (IQR)	4 (3–6)	4 (3–6)	5 (3–6)
Charlson comorbidity index, median (IQR)	5 (4–8)	5 (4–8)	6 (4–9)
Hospital frailty risk score, median (IQR)	5.6 (3.0–8.6)	5.4 (3.0–8.3)	9.3 (6.9–11.9)
CirCom category, n (%)			
0	275,890 (44.0)	262,496 (44.5)	13,394 (37.0)
1 + 0	115,585 (18.5)	109,847 (18.6)	5,738 (15.8)
1 + 1	37,532 (6.0)	35,725 (6.1)	1,807 (5.0)
3 + 0	82,114 (13.1)	76,402 (12.9)	5,712 (15.8)
3 + 1	103,680 (16.6)	95,678 (16.2)	8,002 (22.1)
5 + 0	2,962 (0.5)	2,615 (0.4)	347 (1.0)
5 + 1	8,790 (1.4)	7,580 (1.3)	1,210 (3.3)

CirCom, cirrhosis-specific comorbidity scoring system.

A

Condition	Value
Lymphoma	0.8%
Pulmonary circulation disease	0.9%
Paralysis	2.5%
Chronic blood loss	2.7%
Rheumatoid arthritis/collagen vascular disease	2.8%
Peptic ulcer disease with bleeding	3.0%
Metastatic cancer	3.3%
Solid tumor without metastasis	5.2%
Psychoses	5.2%
Peripheral vascular disease	5.4%
Valvular disease	6.9%
Drug abuse	7.6%
Other neurological disorders	10.6%
Hypothyroidism	13.7%
Weight loss	14.1%
Diabetes without chronic complications	15.3%
Depression	15.5%
Obesity	16.7%
Congestive heart failure	20.3%
Diabetes with chronic complications	22.4%
Chronic pulmonary disease	23.8%
Renal failure	24.4%
Alcohol abuse	32.4%
Deficiency anemias	33.8%
Coagulopathy	39.0%
Fluid electrolyte disorders	51.0%
Hypertension	57.8%

B

Condition	Value
HIV/AIDs	0.8%
Hemi- or paraplegia	1.0%
Rheumatic disease	2.6%
Metastatic solid tumor	3.3%
Dementia	3.6%
Cerebrovascular disease	4.0%
Peptic ulcer disease	4.1%
Myocardial infarction	6.8%
Peripheral vascular disease	6.8%
Any malginancy*	8.0%
Diabetes with chronic complication	16.7%
Diabetes without chronic complication	21.3%
Congestive heart failure	22.3%
Chronic pulmonary disease	24.8%
Renal disease	25.6%

C

Condition	Value
Metastatic cancer	1.9%
Acute myocardial infarction	2.2%
Peripheral arterial disease	2.2%
Epilepsy	4.7%
Substance abuse other than alcoholism	5.1%
Nonmetastatic or hematologic cancer	5.7%
Chronic obstructive pulmonary disease	20.0%
Heart failure	21.0%
Chronic kidney disease	25.3%

D

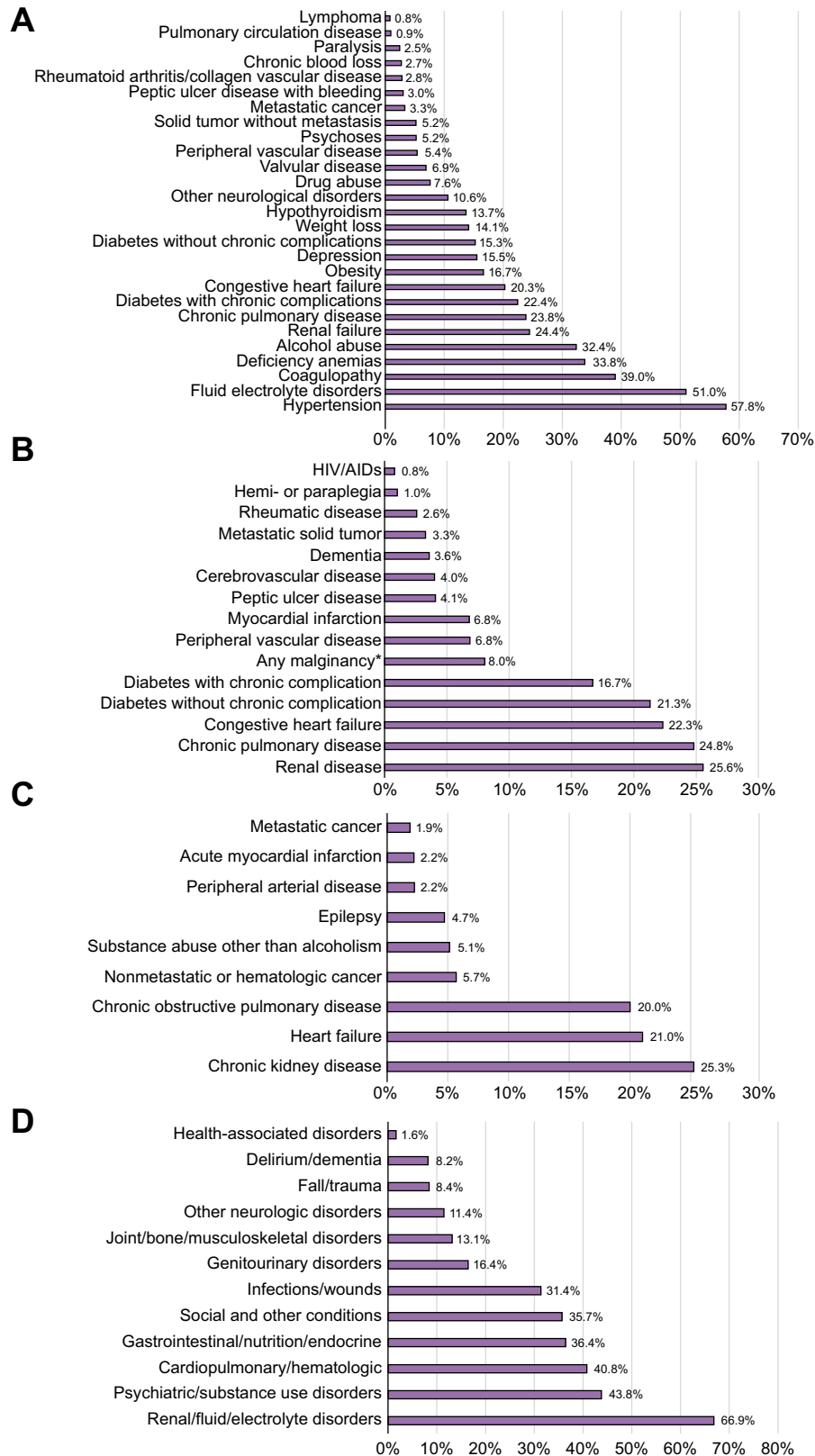| Condition	Value
Health-associated disorders	1.6%
Delirium/dementia	8.2%
Fall/trauma	8.4%
Other neurologic disorders	11.4%
Joint/bone/musculoskeletal disorders	13.1%
Genitourinary disorders	16.4%
Infections/wounds	31.4%
Social and other conditions	35.7%
Gastrointestinal/nutrition/endocrine	36.4%
Cardiopulmonary/hematologic	40.8%
Psychiatric/substance use disorders	43.8%
Renal/fluid/electrolyte disorders	66.9%

Fig. 1. Distribution of the prevalence of comorbid conditions. Distribution of the prevalence of comorbid conditions.as measured by (A) Elixhauser index, (B) Charlson comorbidity index, (C) CirCom, and (D) hospital frailty risk score. CirCom, cirrhosis-specific comorbidity scoring system.
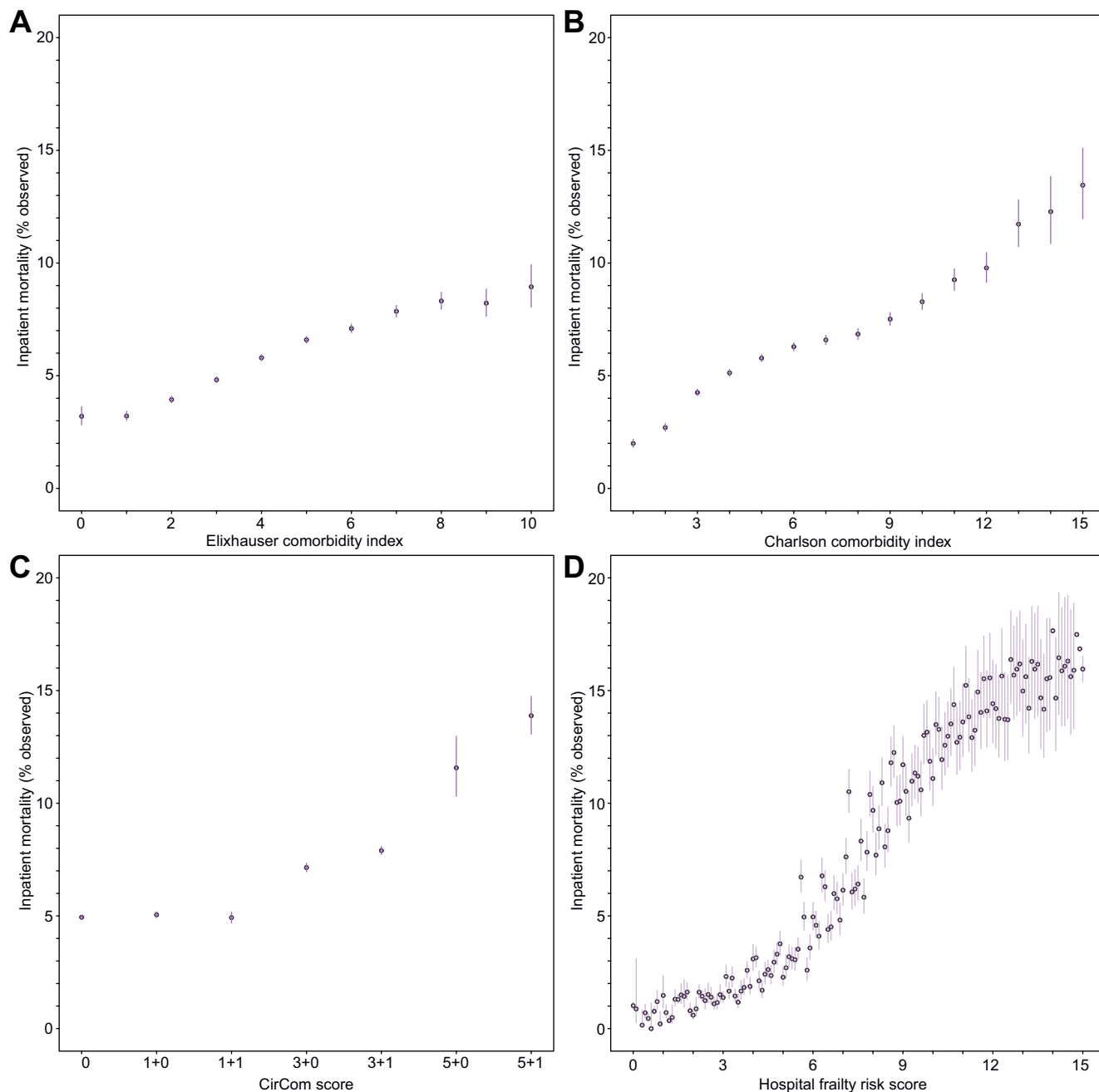
Fig. 2. Distribution of observed mortality by hospital frailty risk score and traditional comorbidity scores. (A) Elixhauser index, (B) Charlson comorbidity index, (C) CirCom, and (D) hospital frailty risk score. CirCom, cirrhosis-specific comorbidity scoring system.

red to blue range of colours). A similar pattern for the range in mortality was observed for CCI and CirCom.

Discussion

Over the last decade, our understanding of the impact of comorbidities on liver disease outcomes has matured. As the cirrhosis population ages and becomes enriched with individuals with metabolic syndrome and its accompanying conditions, risk adjustment in liver disease needs to be reassessed. In the present study, we describe the comorbidity burden in cirrhosis-related admissions as measured by several commonly used risk adjust

ment models (CCI, ECI, and CirCom) as well as HFRS, a newer model developed to identify comorbid conditions linked to adverse outcomes in administrative data. Using any of the models, comorbidity burden in individuals with cirrhosis is high and is associated with increased mortality. Importantly, in this sample of over 600,000 cirrhosis-related hospitalisations, HFRS is a significantly better predictor of mortality compared with CCI, ECI, and CirCom.

In comparing indices, it is critical to understand differences in the comorbidities being measured. In a general medical population, ischaemic heart disease, cancer, and COPD are likely to have the greatest impact on mortality;cirrhosis, mortality may be
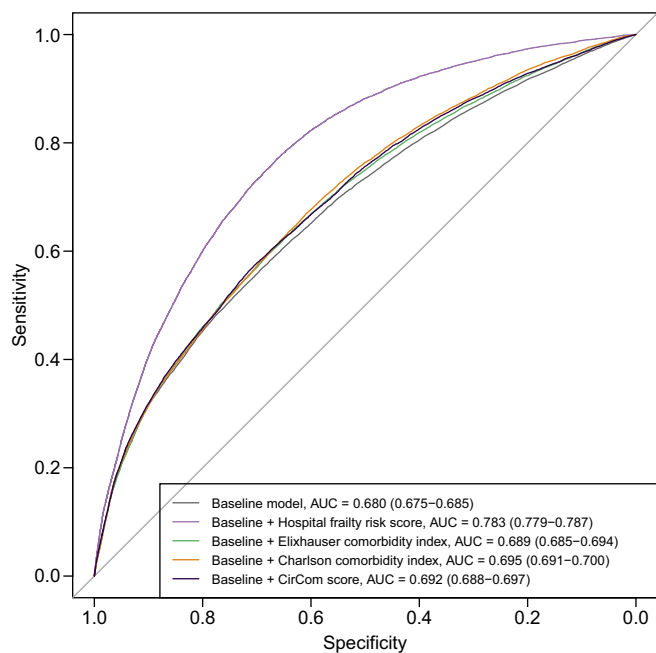
Fig. 3. Receive operator curves depicting the performance of comorbidity indices in predicting inpatient mortality in the validation dataset using a model adjusted for age, sex, ascites, hepatic encephalopathy, and variceal haemorrhage. CirCom, cirrhosis-specific comorbidity scoring system.

influenced more by kidney disease, infections, falls, delirium, and social determinants of health.[25,31–37] Compared with the other indices, HFRS is unique in its inclusion of social conditions, infections, falls/trauma, and dementia/delirium. Furthermore, although kidney disease and/or fluid and electrolyte disorders are present in all four indices, we note striking differences in their prevalence's across the indices. Using HFRS or ECI, over half the study population had codes for this group of comorbid conditions, although this rate was only about 25% for CCI and CirCom. This difference may be explained by CCI's and CirCom's lack of codes for acute kidney injury that are present in HFRS, and the capture of more acute forms of kidney injury may, in part, be responsible for the superior performance of HFRS. Finally, the use of more extensive codes by HFRS (and to a lesser degree by ECI) to identify psychiatric disorders is impactful owing to the high prevalence of these conditions in the population with cirrhosis. Psychiatric conditions contribute to behaviours that cause or worsen underlying chronic liver disease, and alcohol and substance use disorders are becoming more common in this population.[24] Substance use and psychiatric conditions are also in the other indices, but with lower prevalence, and the greater sensitivity of HFRS in identifying these comorbidities may also help explain its performance as a mortality predictor.

egardless of how comorbid conditions are measured, our study confirms that these indices are important predictors of mortality. Specifically, we show that observed mortality increased with increases in each of the indices and inform our understanding of the drivers of poor outcomes associated with decompensated cirrhosis. Here, we noted that the broadest range of mortality was observed when using HFRS, which had the lowest floor and highest ceiling. To explore this finding, we assessed the range of HFRSs and mortality within the range of the other indices. Within ECI, CCI, and CirCom levels, we noted significant variations in mortality that could be identified by HFRS.
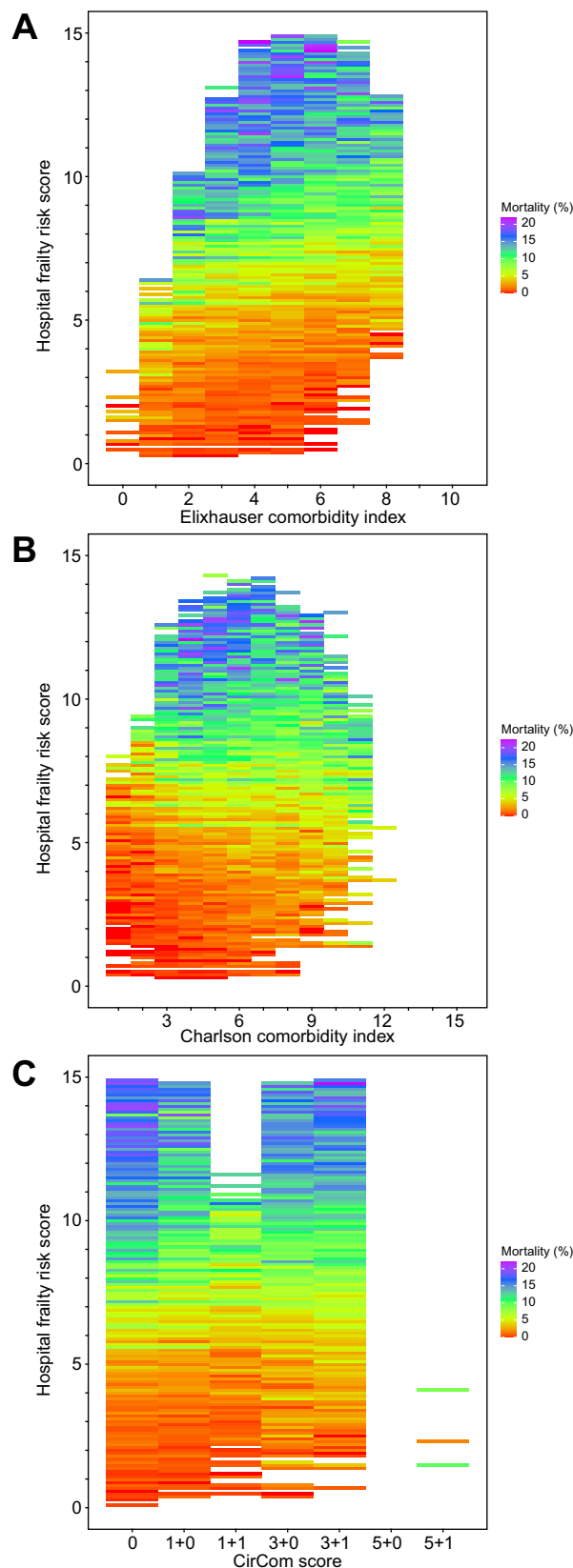

Fig. 4. Distribution of hospital frailty risk score and observed inpatient mortality. Distribution of hospital frailty risk scores and observed inpatient mortality across (A) Elixhauser index, (B) Charlson comorbidity index, (C) CirCom, and (D) hospital frailty risk score. Only combinations with at least 100 observations are shown. CirCom, cirrhosis-specific comorbidity scoring system.

In contrast, at each HFRS of the study cohort, there was a significant range in mortality within ECI groups. In fact, even those with an ECI or CCI of 0 or a CirCom score of 0 + 0 have additional conditions identified by HFRS that are associated with mortality. Although our study is the first to show the superior performance of HFRS compared with ECI, CCI and CirCom, it is not the first study to examine the performance of HFRS in a liver disease population. A prior study also demonstrated the superiority of HFRS over the clinical frailty index, another administrative frailty index using 52 ICD codes and 25 procedures codes.[18] Finally, it is important to note that adding ascites and the other complications of portal hypertension to the prediction model did improve the performance of each comorbidity index, the AUCs were highest for those with both the cirrhosis complications and comorbidity index, indicating that these comorbidities capture additional aspects of cirrhosis-related care that are relevant to outcomes yet not flagged by diagnosis codes used for traditional cirrhosis complications.

The impact of our results should be interpreted with several limitations in mind. First, owing to the nature of the dataset, we are able to test the models only on inpatient mortality. Model performance in prediction of mortality 30 or 90 days from hospitalisation is likely different and will need to be assessed in future studies. Second, the original HFRS was developed using 2 years of administrative data leading up the hospital encounter. For this study, we were limited to the codes available for the individual encounter. It is possible that HFRS performance will be different when used in datasets with longitudinal collection of diagnosis codes. We hypothesise that availability of more diagnosis codes over time would only improve model performance. Furthermore, it is important to note that even without continuous data over 2 years, HFRS proved to be an important predictor of inpatient mortality, and this modified version of HFRS may be a useful tool for measuring and cataloguing co-existing conditions.[19] Similarly, performance of risk adjustment models in administrative datasets might be different than those in electronic health record-based datasets. Although these assumptions need to be tested in future studies, we anticipate that these limitations would not change our overall conclusions.

In conclusion, this study is an important step forward in our understanding of how best to risk adjust when examining mortality in individuals with cirrhosis. Risk assessment tools such as CCI, ECI, and CirCom remain valuable in predicting outcomes in the current era, but compared with these tools, HFRS may offer several advantages when applied to administrative datasets. Future work validating these findings in other datasets may also provide insights into which comorbid conditions could be targeted in efforts to improve outcomes in individuals with cirrhosis.

Abbreviations

CCI, Charlson comorbidity index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECI, Elixhauser comorbidity index; GAM, generalised additive model; HCUP, Healthcare Cost and Utilization Project; HFRS, hospital frailty risk score; NIS, National Inpatient Sample.

Conflicts of interest

The authors declare that they have no conflict of interest. For full disclosure, NC serves as a paid consultant to Madrigal, Zydus, Galectin, Altimmune, GSK, Merck, Pfizer, Foresite, and Ventyx. He has research funding from Galectin, DSM, and Exact Sciences and has equity in BendaSaion, a contract research organisation.

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

Authors' contributions

Study concept and design: EO, AD. Data analysis: SK, AD, EO. Manuscript preparation: AD, EO, SP. Critical manuscript review: all authors.

Data availability statement

The analytic methods used in this study are detailed in the Patients and Methods section. The data will not be made publicly available by the research team but are available from the from Healthcare Cost and Utilization Project.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100955.

References

Author names in bold designate shared co-first authorship

[1] Shearer JE, Gonzalez JJ, Min T, et al. Systematic review: development of a consensus code set to identify cirrhosis in electronic health records. Aliment Pharmacol Ther 2022;55:645–657.

[2] Dahiya M, Eboreime E, Hyde A, et al. International Classification of Diseases codes are useful in identifying cirrhosis in administrative databases. Dig Dis Sci 2022;67:2114–2122.

[3] Bloom PP, Tapper EB. The use of administrative data to investigate the population burden of hepatic encephalopathy. J Clin Med 2020;9.

[4] Hagström H, Adams LA, Allen AM, et al. Administrative coding in electronic health care record-based research of NAFLD: an expert panel consensus statement. Hepatology 2021;74:474–482.

[5] Myers RP, Quan H, Hubbard JN, et al. Predicting in-hospital mortality in patients with cirrhosis: results differ across risk adjustment methods. Hepatology 2009;49:568–577.

[6] Myers RP, Hubbard JN, Shaheen AA, et al. Hospital performance reports based on severity adjusted mortality rates in patients with cirrhosis depend on the method of risk adjustment. Ann Hepatol 2012;11:526–535.

[7] Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care 1998;36:8–27.

[8] Deyo R, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.

[9] Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. Gastroenterology 2014;146:147–156. quiz e115-146.

[10] Pefoyo AJ, Bronskill SE, Gruneir A, et al. The increasing burden and complexity of multimorbidity. BMC Public Health 2015;15:415.

[11] Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Med Care 2012;50:1109–1118.

[12] Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–M94.

[13] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.

[14] **Lai JC**, **Tandon P**, Bernal W, et al. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74:1611–1644.

[15] Tandon P, Montano-Loza AJ, Lai JC, et al. Sarcopenia and frailty in decompensated cirrhosis. J Hepatol 2021;75(Suppl. 1):S147–S162.

[16] Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018;391:1775–1782.

[17] Kim DH, Schneeweiss S, Glynn RJ, et al. Measuring frailty in medicare data: development and validation of a claims-based frailty index. J Gerontol A Biol Sci Med Sci 2018;73:980–987.

[18] Louissaint J, Murphy SL, Sonnenday CJ, et al. Applying administrative data-based coding algorithms for frailty in patients with cirrhosis. Liver Transpl 2021.

[19] Louissaint J, Tapper EB. A claims-based frailty risk score is associated with hospitalization for acute-on-chronic liver failure: but is it frailty? Liver Transpl 2021;27:9–11.

[20] Mahmud N, Kaplan DE, Taddei TH, et al. Frailty is a risk factor for post-operative mortality in patients with cirrhosis undergoing diverse major surgeries. Liver Transpl 2020.

[21] Shah S, Goldberg DS, Kaplan DE, et al. Patient frailty is independently associated with the risk of hospitalization for acute-on-chronic liver failure. Liver Transpl 2020:1–11.

[22] Healthcare Cost and Utilization Project: quality control procedures. 2022. Available from: https://hcup-us.ahrq.gov/db/quality.jsp. [Accessed 10 April 2022].

[23] Healthcare Cost and Utilization Project: NIS database documentation. 2019. Available from: https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp. [Accessed 1 May 2019].

[24] Desai AP, Greene M, Nephew LD, et al. Contemporary trends in hospitalizations for comorbid chronic liver disease and substance use disorders. Clin Transl Gastroenterol 2021;12:e00372.

[25] Desai AP, Knapp SM, Orman ES, et al. Changing epidemiology and outcomes of acute kidney injury in hospitalized patients with cirrhosis – a US population-based study. J Hepatol 2020;73:1092–1099.

[26] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–1139.

[27] Healthcare Cost and utilization Project: elixhauser comorbidity software, Version 3.7 Available from:https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp. [Accessed 1 May 2019].

[28] Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Stat Sci 2001;16.

[29] Dorai-Raj S. Binom: binomial confidence intervals for several parameterizations. R package version 1.1-1. 2014. Available from: https://CRAN.R-project.org/package=binom. [accessed February 2021].

[30] Wood SN. Generalized Additive Models. 2017.

[31] Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. JAMA 2018;319:1444–1472.

[32] Shankar N, Ramani A, Griffin C, et al. Extrahepatic causes of death in cirrhosis compared to other chronic conditions in the United States, 1999–2017. Ann Hepatol 2021;26:100565.

[33] Nadim MK, Garcia-Tsao G. Acute kidney injury in patients with cirrhosis. N Engl J Med 2023;388:733–745.

[34] Ha A, Saleh ZM, Serper M, et al. Falls are an underappreciated driver of morbidity and mortality in cirrhosis. Clin Liver Dis (Hoboken) 2022;20:146–150.

[35] Desai AP, Gandhi D, Xu C, et al. Confusion assessment method accurately screens for hepatic encephalopathy and predicts short-term mortality in hospitalized patients with cirrhosis. Metab Brain Dis 2022.

[36] Mohamed KA, Ghabril M, Desai A, et al. Neighborhood poverty is associated with failure to be waitlisted and death during liver transplantation evaluation. Liver Transpl 2022;28:1441–1453.

[37] Bajaj JS, Lai JC, Tandon P, et al. Role of oral health, frailty, and minimal hepatic encephalopathy in the risk of hospitalization: a prospective multi-center cohort of outpatients with cirrhosis. Clin Gastroenterol Hepatol 2022.