Received: 29 May 2022 | First decision: 13 July 2022 | Accepted: 11 November 2022

DOI: 10.1111/apt.17324

AP&T Alimentary Pharmacology & Therapeutics WILEY

Systematic review: the role of frailty in advanced chronic liver disease

Sarah P. Bowers[1,2] | Paul N. Brennan[2,3] | John F. Dillon[1,2]

[1]NHS Tayside, Ninewells Hospital and Medical School, Dundee, UK

[2]Department of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK

[3]Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, UK

Correspondence
Sarah P. Bowers, NHS Tayside, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK.
Email: sarah.bowers3@nhs.scot

Summary

Background: Frailty is a known predictor of outcome and mortality in patients undergoing liver transplantation. However, most patients remain unsuitable transplant candidates. It is not yet known if the assessment of frailty in non-transplant candidates can aid prognostication.

Aim: To collate and interrogate the various frailty tools presently used to predict mortality in the non-transplant cirrhosis setting.

Methods: A comprehensive review of MEDLINE and EMBASE databases for articles published from inception to March 2022 was undertaken, excluding those where patients underwent transplantation or had hepatocellular carcinoma.

Results: We identified 12 observational cohort studies, featuring 9 frailty indices. These were from various global healthcare settings and of fair or good quality. Most were objective tools utilising clinician-based assessments. All frailty scores predicted prognosis, with variability in the method of application, and utilisation in long- or short-term mortality. Three studies directly compared different indices in the same population. There was some evidence that simple tools could perform as well, if not better, than more complex, time-consuming scores.

Conclusions: Various frailty tools can reproducibly evaluate mortality in patients with cirrhosis who are ineligible for transplant. However, further prospective head-to-head comparative studies are needed. In addition to determining model utility, studies should focus on important relative considerations which may limit widespread implementation including, ease of use and limited resources, given the global disparity of liver care provision. These tools may positively identify specific patient cohorts at risk of impending deterioration, thereby stratifying those patients likely to benefit from early integration with palliative care.

The Handling Editor for this article was Dr Rohit Loomba, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Liver disease accounts for over 2 million deaths per year worldwide, with half of these being attributed to cirrhosis, which is the 11th most common cause of death.[1] In contrast to most other malignant and non-malignant conditions, deaths from liver disease have risen in the United Kingdom, particularly in those under 65.[2] Morbidity and mortality from liver disease disproportionately affect those of working age, with liver disease accounting for an estimated 62,000 years of working life lost in the UK alone.[3] Furthermore, cirrhosis impairs health-related quality of life including mental health and physical factors and reduces the ability to perform activities of daily living (ADL).[4–6]

Presently, there are no approved pharmacological therapies for reversing fibrosis which results in cirrhosis, with liver transplantation remaining the only curative option for those with end-stage cirrhosis or hepatocellular carcinoma (HCC). Unfortunately, many patients will be too sick or have advanced co-morbidities that would preclude transplant referral, while a significant proportion of those referred for transplant assessment are ineligible. Among those patients listed for transplantation, around 7% die annually while on the waiting list in the UK.[7] There is an inherent mismatch in those patients necessitating liver transplantation, compared to the available organs donated, in spite of the use of split grafting and living donor alternatives to traditional orthotopic liver transplant using cadaveric organs.

The current most commonly employed prognostication tools for stratification of liver disease severity are Child-Pugh and MELD; both initially designed to predict mortality in those undergoing surgical or radiological interventions for portal hypertension.[8–10] These tools were adapted into clinical practice for both identifying eligibility, and waitlist prioritisation for transplantation, as well as being used for general prognostication. However, there have been criticisms of these tools. Child-Pugh includes subjective markers (ascites and encephalopathy) which can lead to inter-rater variability.[11,12] Both tools utilise INR, which is poorly representative of true coagulopathy, and is subject to inter-laboratory variation within laboratory systems.[13,14] Whilst they both have been shown to have the predictive capability in prognosis, there is a large variance between them in prognosticating complex clinical circumstances, e.g. mortality in ICU and in those undergoing surgery.[11,15] Newer advances in the assessment of clinical biomarkers and their utility in prognosis remain unvalidated, while often necessitating, invasive testing methods and are limited to resource-rich settings.[16,17] There has been a number of studies assessing the prognostic ability of these tools, highlighting the uncertainty and limitations of those currently applied.[18]

This leads to a need to develop alternative approaches for which frailty has been considered a key composite. The concept of frailty was originally derived in a geriatric population, where it was explored as an age-related biologic syndrome of decreased reserve and resistance to stressors. Resultantly, frailty is characterised by cumulative declines across multiple physiological systems and increased vulnerability to adverse outcomes.[19,20] A recent systematic review revealed that there were no frailty indices specifically developed or validated for younger populations, however, there was evidence that some existing markers of frailty had predictive ability in this group.[21]

The role of frailty in liver disease has been established for decades, with the original Child score using 'nutritional status' before it was replaced with prothrombin time by Pugh.[8,9] The pathophysiology of frailty in liver disease remains complex and is increasingly appreciated as a multisystem sequela. Presently, there are a number of putative theories existing around decreasing synthetic liver function causing resultant multisystem dysfunction with relative immunocompromise, as well as endocrine, gut microbiome, skeletal and neuromuscular maladaptation.[22,23] An estimated 17%–43% of those with cirrhosis and 25% on liver transplant waiting lists are identified as frail.[22,24] Frailty has also repeatedly been demonstrated to be an independent predictor of hepatic decompensation, hospitalisation, transplant delisting and post-transplant complications.[22,25,26]

Indeed, much of the research around frailty assessment in cirrhosis has been undertaken in the context of transplantation. However, only a minority of patients are eligible for a liver transplant, owing primarily to ongoing alcohol or substance misuse, poor performance status or co-morbidities—all of which can contribute to frailty. In 2016–2017, 14,696 deaths related to liver disease were recorded in the United Kingdom[3]; during the same time interval, only 980 liver transplants were undertaken.[7]

Therefore, the vast majority of patients with end-stage liver disease are managed conservatively. Existing tools for predicting mortality in liver disease, namely, Child-Pugh and MELD, are aimed to identify patients for aggressive attempts at curative transplantation and fail to holistically assess the patient as a whole. They also do not necessarily relate to patient needs or quality of life thus leaving a gap and problem in identifying patients who could be treated with more palliative intent earlier in the process.[27,28] To date, there have been no identified reviews assessing the ability of existing measurements of frailty to predict prognosis in patients with end-stage liver disease, who are unsuitable for transplantation. This review aims to understand the role that existing frailty tools may have in prognosticating in such persons.

2 | METHODS

This systematic review protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[29] and was prospectively registered with PROSPERO: CRD42021246932.[30]

2.1 | Search strategy

SPB performed a comprehensive literature search of peer-reviewed articles from MEDLINE and EMBASE from inception to 12 March 2022. Key search terms were used for 'cirrhosis' or 'chronic liver disease'; 'frailty' and 'prognosis', 'mortality' or 'survival' through

a joint agreement with all researchers and appropriate Medical Subheadings (MeSH) terms were identified for each journal.

2.2 | Study selection

Searches were limited to English language, original research studies that reported the ability of markers/assessment of frailty phenotype, frailty index or discrete marker of frailty to predict prognosis in adult patients with cirrhosis of any cause who were not being assessed for transplantation or actively on the transplant list. Studies could be prospective or retrospective. Studies that solely included patients on the transplant list or with hepatocellular carcinoma were excluded. If there were studies using a variety of patients eligible and ineligible for transplantation, these were included if it was possible to distinguish the data for the non-transplant group.

Search results were managed using Endnote. These were combined, deduplicated, screened for study type and title/abstract reviewed by SPB with corroboration with PNB, and disagreements brought to JFD. Full texts were then reviewed separately by authors; SPB and PNB before consensus was agreed. Study selection is outlined in Figure 1.

2.3 | Data extraction

The following data were extracted and tabulated by SPB and PNB for each final included study: year of publication, country, setting (inpatient, outpatient, mixed), study design, sample size, gender, mean/median MELD, a measure of frailty used, length of follow-up and impact on prognosis. Due to varying ways of statistically measuring prognostication ability, these were described descriptively. Consideration was given to the ability to perform meta-analysis however due to the variability in statistical analysis this was not felt to be achievable in the scope of this review.

2.4 | Quality assessment

We evaluated the methodological quality using the National Heart, Lung and Blood Institute, National Institute for Health quality assessment tool for observational cohort and case–control studies (NHLBI). Inter-observer agreement between SPB and PNB was 90%.

3 | RESULTS

After study selection (Figure 1), a total of 12 papers, featuring 9 frailty indices, were included in the final analysis—summarised in Table 1. All of these were observational cohort studies. Four studies were from the United States of America, 2 from China, 2 from Europe (Spain and Slovakia), 1 from Chile and 1 from Egypt. A total of 19,394 patients were included across the 12 final studies (range 113–16,561). The mean reported MELD was 12.15 (range 7.5–17.9). Eight studies explored inpatient populations, with the remaining 4 focussing on outpatients. The studies that were assessed were exclusively observational or cohort studies, with no defined interventions in any of the studies. Using the suitable quality assessment tool,[31] only one of these studies[32] was highlighted as poor quality.

3.1 | Objective assessment of frailty

Five frailty indices comprising objective markers of frailty were examined in 9 studies.

3.1.1 | Liver Frailty Index

The Liver Frailty Index (LFI) utilises grip strength, chair stands and balance assessment to assess frailty and was originally developed to assess mortality among patients on the liver transplant waitlist. Scores are calculated via an online calculator and a score of ≥4.5 categorises an individual as frail.[33] There were two prospective comparative studies comparing LFI, Short Physical Performance Battery (SPPB), Clinical Frailty Score (CFS) and Fried Frailty Index (FFI)—Skaldany et al.[34] in the inpatient setting and Singh et al.[35] in outpatients. In the inpatient study,[34] LFI was consistently reliable in predicting mortality across different time points and had the highest predictive value for mortality at 180 days (AUROC 0.777, 95% CI 0.705–0.839) compared to the others (CFS = 0.763, SPPB = 0.747, FFS = 0.711). Although in the outpatient setting,[35] there was no statistical significance in the mortality predictive ability of the scores, LFI had the maximum AUC of 0.97.

3.1.2 | Short Physical Performance Battery

The SPPB was originally developed in three communities in the United States of America with patients over 65 completing a series of tests consisting of standing balance, walking speed and chair stands with a score of <7 representing frailty.[36] It has previously been shown to be predictive of both frailty and waitlist mortality in patients awaiting a liver transplant.[37] Four of the included 12 studies prospectively utilised SPPB in their assessment and demonstrated that it could predict mortality.[32,34,35,38] Essam Behiry et al.[32] demonstrated through ROC curve analyses of mortality based on frailty as per SPPB, handgrip, MELD and Childs-Pugh that only SPPB had a significant AUC (0.743; $p = 0.013$). In an evaluation of SPPB compared to CFS, Tandon et al.[38] found CFS to be superior at predicting 6-month mortality (odds ratio = 5 for CFS vs OR = 3.4 for SPPB) and commented that CFS was more user-friendly and less time-consuming. Similarly, as above, Skladany et al.[34] and Singh et al.[35] demonstrated that there were other frailty indices which outperformed SPPB.

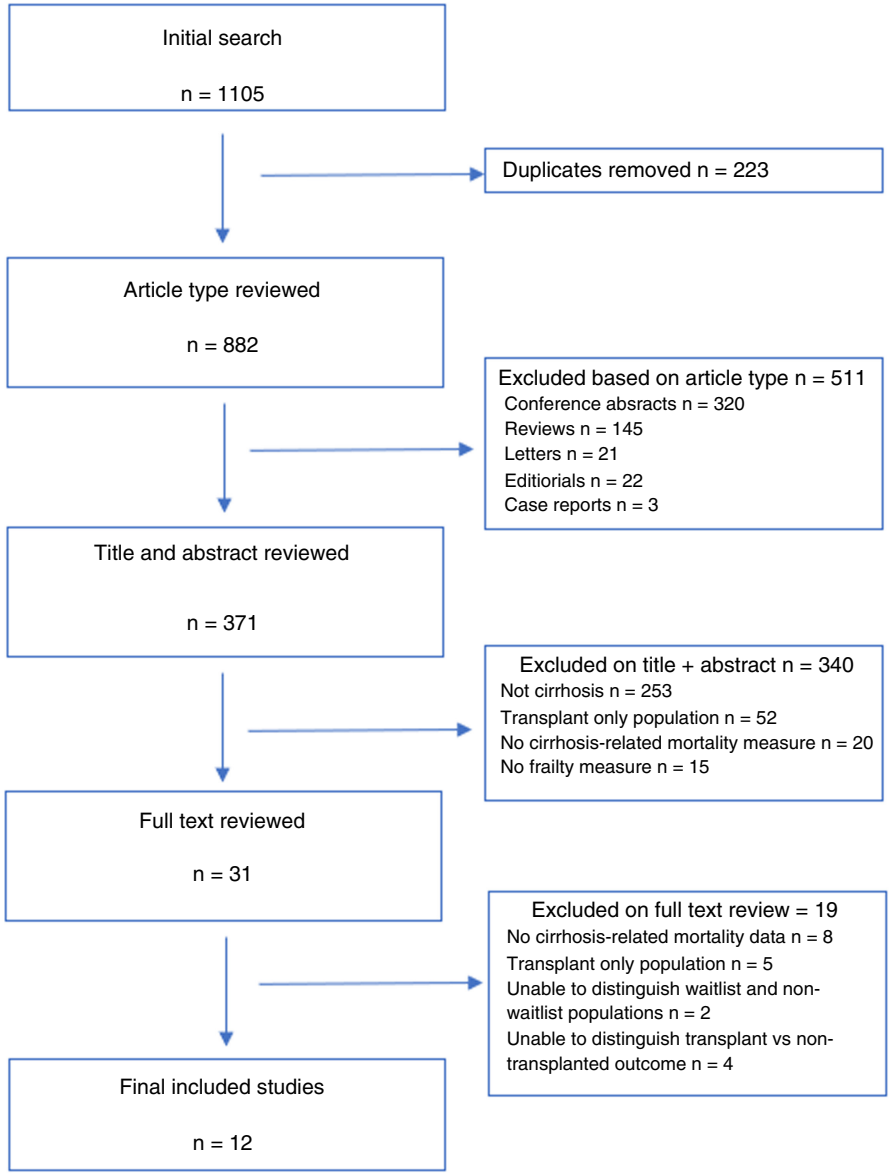

FIGURE 1 Study selection flowchart

3.1.3 | Five-metre gait speed

Gait speed has been found to be the best validated functional performance estimation in pharmacological trials for both frailty and sarcopenia.[38] 5-metre gait speed (5MGS) had previously been validated as an independent predictor of cirrhosis complications requiring hospitalisation[26] but its role in mortality prediction had not previously been explored. Both Deng et al.[40] and Wang et al.[39] prospectively demonstrated the ability of 5MGS to predict all-cause mortality. This was consistently proven as both a continuous variable (hazard ratio = 0.133) and in binary variables (slow 5MGS [0.8 ms^{-1}] HR = 4.805).[40] Addition of 5MGS to MELD scoring in both cohorts improved the discriminatory power of MELD: Deng et al.[40] demonstrated AUC improved from 0.724 to 0.802 with the addition of 5MGS and Wang et al.[39] showed the addition of 5MGS alongside albumin to MELD yielded a C index of 0.804.

3.1.4 | Routine nursing assessments

Tapper et al.[40] retrospectively utilised nursing assessments (ability to perform ADLs; Braden scale for predicting pressure ulcer risk; and Morse fall risk score), which are already part of routine American clinical practice to encapsulate frailty. Poorer ADL function was most associated with increased 90-day mortality (OR = 3.84; 95% CI 2.60–5.67); Braden score was associated with increased risk to a lesser degree (OR = 3.40, 1.90–6.07), and there was no association with Morse score (OR = 1.01, 1.01–1.02).

3.1.5 | Hospital Frailty Risk Score

The Hospital Frailty Risk Score (HFRS) was developed using International Classification of Diseases (ICD-10) administrative data to calculate a score by giving each diagnostic code a weighting, with

TABLE 1 Summary of included studies

Reference	Frailty tool used	Study design	Measure of frailty	N	Setting	Country	MELD	Length of follow-up	Impact on prognosis/ mortality	Quality
Deng et al., *Ther Adv Chronic Dis* 2020; 11: 1–11	5-metre gait speed (5MGS)	Prospective observational cohort study	Objective	113	Inpatient	China	Mean: 11.4 (+ − 4.7)	2 years	5MGS able to predict mortality as both binary and continuous variable. Improves the discriminatory ability of MELD-Na.	Fair
Deng et al., *Ann Transl Med* 2020; 8(19): 1217	Modified Caroline Frailty Index	Prospective observational cohort study	Subjective	158	Inpatient	China	Median: 11 (8–13)	2 years	FI did not impact on 90-day survival however was able to predict 1-year and 2-year mortality.	Fair
Essam Behiry et al., *Int J Hepatol.* 2019;2019:8092865	Short Physical Performance Battery	Prospective observational cohort study	Objective	145	Inpatient	Egypt	Mean: 16 (+ − 6)	3 months	SPPB performed better than MELD and Child-Pugh score in predicting mortality.	Poor
Román et al., *Liver Int* 2021; 41(2): 357–68	Fried Frailty Index	Prospective observational cohort study	Subjective	135	Outpatient	Spain	Mean 9.6 (3.6)	2 years	FFI did not show ability to predict mortality.	Fair
Shah et al., *Liver Transplantation* 2021; 27: 16–26	Hospital Frailty Risk Score (HFRS)	Retrospective observational cohort study	Objective	16,561	Inpatient	USA	Median: 7.5 (6–14)	90 days	HFRS not associated with 30- or 90-day mortality	Fair
Singh et al., *J Clin Exp Hepatol* 2022; 12(2): 398–408	Liver Frailty Index Short Physical Performance Battery Fried Frailty Index Clinical Frailty Scale	Prospective observational cohort study	Objective (LFI and SPPB) Subjective (FFI and CFS)	116	Outpatient	India	Median16 (14.9–17)	6 months	All tools were able to predict mortality with no significant difference in discriminatory value between them (though LFI was noted to have the maximum AUC)	Good
Skladany et al., *Croat Med J.* 2021;62(1):8–16.	Liver Frailty Index Clinical Frailty Scale Fried Frailty Index Short Physical Performance Battery	Prospective observational cohort study	Objective (LFI and SPPB) Subjective (CFS and FFI)	168	Inpatient	Slovakia	Median: 16 (IQR = 9)	300 days	All frailty assessment tools were significant predictors of mortality. LFI alone and LFI combined with MELD had the highest numerical predictive value for death	Fair
Soto et al., *Ann Hepatol.* 2021;25:100327.	Fried Frailty Index	Prospective observational cohort study	Combined	126	Outpatient	Chile	Median: 13 (11–16)	4 years	Cumulative incidence of mortality higher in frail patients compared to non-frail patients as per FFI.	Fair
Tandon et al., *Am J Gastroenterol* 2016; 111: 1759–1767	Clinical Frailty Scale Friend Frailty Index Short Physical Performance Battery	Prospective observational cohort study	Objective (SPPB) Subjective (CFS and FFI)	300	Outpatient	USA	Mean: 12 (4.8)	6 months	All frailty assessment tools were significant predictors of mortality	Good

(Continues)

TABLE 1 (Continued)

Reference	Frailty tool used	Study design	Measure of frailty	N	Setting	Country	MELD	Length of follow-up	Impact on prognosis/ mortality	Quality
Tapper et al., *Hepatology* 2015;62(2):584–90.	Routine nursing assessments: activities of daily living (ADLs), Braden scale, Morse fall risk score	Retrospective observational cohort study	Objective	734	Inpatient	USA	Mean: 17.9 (7.5)	90 days	Ability to perform ADLs was related to 90-day mortality and was poorer in the encephalopathic group	Good
Tandon et al, *Hepatology* 2017; 65(1): 217–224	Karnofsky Performance Scale, age, MELD model (KAM)	Prospective observational cohort study	Combined	954	Inpatient	USA	Median: 17 (13–21)	3 months	KPS tertile predicted mortality with statistical significance. KPS improved the discriminatory ability of age and MELD	Fair
Wang et al., *Postgrad Med* 2021; 133(60): 680–687	5 m gait speed (5MGS)	Prospective observational cohort study	Objective	113	Inpatient	China	Median: 8 (11–13.5)	2 years	5MGS could independently predict 2-year mortality. The predictive ability of 5MGS was improved with addition of albumin and MELD-Na score	Fair

a score of >15 indicating high-risk frailty. It was designed in an attempt to minimise the potential for inter-operator variability that could arise from other frailty tools.[41] Shah et al.[42] undertook the first retrospective evaluation of the HFRS in 16,561 incident admissions with acute-on-chronic liver failure. There was no association between HFRS and ACLF-specific short-term mortality ($p = 0.33$ at 90 days) in this group though it did confer an ability to predict poorer long-term survival from time of hospitalisation (HR 1.02 per 5-point increase in score, 95%CI 1.01–1.03). It has been previously acknowledged that HFRS can misclassify younger patients as frail compared to other frailty tools[43] which may impact its discriminatory ability in chronic liver disease.

3.2 | Subjective assessment of frailty

Three of the included studies explored two models of subjectively defined criteria to indicate frailty. These were a variety of healthcare professionals classified and self-reported.

3.2.1 | Clinical frailty scale

The Clinical Frailty Scale (CFS) is a 7-point scale originally created in a cohort of elderly patients via the Canadian Study of Health and Aging and is designed to be an easy, quick-to-use assessment of global frailty categorising patients into 1–9 identified categories ranging from 1: very fit to 9: terminally ill.[44] It had not been validated in patients with cirrhosis prior to Tandon et al.[45] who utilised this tool to prospectively assess 330 outpatients with cirrhosis for risk of death and unplanned hospitalisation, alongside FFI and SPPB and demonstrated a dose-dependent ability of CFS to better discriminate than the other indices. Skaldany et al.[34] commented that CFS in their prospective study of mortality risk in hospitalised patients with cirrhosis had the highest prognostic value (compared with LFI, SPPB and FFI) for mortality during the hospital admission and at 30 days (AUC = 0.864) and 90 days (AUC = 0.778), though as discussed prior LFI performed better overall. As before, Singh et al.[35] prospectively found CFS could predict mortality in an outpatient cohort with no statistical difference to LFI or other parameters.

3.2.2 | Modified Carolina Frailty Index

In an attempt to lessen the time burden associated with longer clinician-assessed frailty indices with physical measurements, Deng et al.[46] developed a self-reported frailty tool from the Carolina Frailty Index—a 36-item self-assessment tool initially developed to identify frailty (score of >0.38) in elderly patients with cancer.[47] The final questionnaire consisted of a series of questions to identify limitations in ADL, physical function, unintentional weight loss, exhaustion, depression and social activities. In cirrhosis, the modified Caroline Frailty Index (mCFI) was prospectively unable to predict 30-day mortality ($p = 0.104$) but long-term mortality could be predicted at both 1 year ($p = 0.011$) and 2 year ($p = 0.0044$).

3.3 | Combined subjective and objective assessments

Six of the included studies utilised combined objective and subjective markers for frailty assessment as demonstrated through 2 indices.

3.3.1 | KAM model

Originally derived from patients with malignancy, the Karnofsky Performance Status (KPS) has been validated across many chronic disease populations, and more recently, Orman et al.[48] demonstrated it to be a predictor of liver transplant waitlist mortality. Tandon et al.[49] prospectively evaluated self-reported KPS in non-electively admitted cirrhosis patients; 17% had low KPS scores, consistent with an inability to care for oneself—considerably worse than noted on the transplant waiting list—and this was associated with 3-month mortality.[48] Multivariate analysis identified KPS, age and MELD to be independent predictors of mortality in the cohort and the team proposed the KAM model (KPS, age and MELD) which was found to be superior to the individual markers in predicting 3-month mortality with an AUC of 0.74 (95% CI 0.68–0.79).

3.3.2 | Fried Frailty Index

Four of the included studies prospectively analysed the FFI which was adopted from geriatric medicine and is a five-domain score: unintentional weight loss, reduced handgrip strength, slow walking speed, self-reported exhaustion and low physical activity. [50] A score of 3–5 indicates frailty. It was previously validated in a transplant waitlist population.[37] In a cohort of outpatients with reasonably well-preserved synthetic liver function and mean MELD of 9.6 FFI did not demonstrate mortality predictive ability (11.4% of frail participants died at 2 years vs 8% on non-frail, $p = 0.50$).[51] Three further inpatient studies[35,38,53] showed the discriminatory ability of FFI to predict mortality although it produced the lowest numerical prognostic value compared when evaluated alongside other scores (LFI, CFS, SPPB).

4 | DISCUSSION

This review identifies a variety of different methods for assessing frailty in the non-transplant setting through objective and subjective assessments, in both inpatients and outpatients. There were nine identified frailty indices explored in the 12 included observational studies. Most of the included studies examined individual frailty scores with only 3 comparing assessments—Skladany et al.[34] compared LFI, SPPB, FFI and CFS in inpatients; Singh et al.[35] compared LFI, SPPB, FFI and CFS in outpatients and Tandon et al.[41] compared LFI, SPPB and CFS in outpatients. Most of the included frailty indices were already established scores from other settings, either originating from transplanted populations (LFI) or geriatric populations (CFS, FFI, SPPB, 5MGS, HFRS, mCFI, routine nursing assessments); only one of the included studies developed a new model for frailty to predict mortality (KAM). All scores demonstrated the ability to predict prognosis, with variability in the method of application regarding cohort setting, and the ability to predict long- or short-term mortality.

It is challenging to compare individual frailty indices from studies in different countries and clinical settings. However, in two of the comparative studies; the LFI had the highest numerical value compared to objective (SPPB), subjective (CFS) and combined frailty assessment tools (FFI).[34,35] The LFI is a purely objective assessment based on formally assessed physical indicators of frailty: grip strength, chair stands and balance. Its high performance in predicting mortality highlights the role that formal assessment of frailty by trained professionals can have in identifying those who are frail. However, this formal objective assessment does require training and with time and resource constraints in the clinical setting, may not be easily reproducible. The included subjective markers were a mixture of clinician-assessed (CFS) and patient-reported (mCFI). Skladany et al. analysed CFS alongside the more objective markers LFI, FFI and SPPB[34] and showed it to have the highest prognostic value for mortality during hospital stay, 30- and 90-days though LFI performed more consistently and to a higher numerical value overall. Furthermore, CFS has been shown to be predictive of the end point of mortality or transplant, irrespective of muscle mass[52] suggesting it may encapsulate the multifactorial composites of frailty in cirrhosis. This limited evidence does perhaps demonstrate the power of an easy-to-apply scoring system, thereby minimising clinician time and training.

Within the liver transplant setting, frailty is an established part of patient assessment and selection. This is due to the consistently proven relationship between increasing frailty and mortality after transplant.[53,54] The role of 'prehabilitation' is increasing wherein patients identified as frail receive physical or nutritional intervention to improve outcomes after transplantation.[55–57] This important intervention will hopefully improve the suitability of some patients for transplantation thus allowing them the opportunity for the continued only option for cure from cirrhosis. Despite attempts to improve the availability of donated livers by research into donation after circulatory death, the outcomes remain poor[58] meaning that unfortunately cure through liver transplantation continues to only be an option for a minority of patients.

Going forward, it is therefore imperative that comprehensive methods of accurately predicting prognosis beyond the transplant setting are explored since those ineligible for transplant with decompensated cirrhosis have a median survival of 2 years.[19] The ability of the various frailty indices in this review to predict mortality furthermore emphasises that those ineligible for transplant have worse health outcomes. There is an emerging understanding of the needs of frail patients who are approaching the end of life, and although they are acknowledged to have complex physical, psychosocial and supportive needs, they have inequitable access to palliative

care services.[59,60] Additionally, patients with advanced cirrhosis are rarely referred for specialist palliative care, and when this does occur, it is often too late.[27,61] Poonja et al. demonstrated that less than 10% of those denied liver transplantation received a referral for palliative care services, despite their poor clinical prognosis.[62] Therefore, early identification of those with advanced cirrhosis with a frail phenotype who are ineligible for liver transplantation is vital. This would clearly allow for a comprehensive assessment of palliative care needs in this group and may prompt specialist palliative care referral. Such proactive approaches are likely to be necessary and will allow the development of dedicated pathways of care to better serve these patient groups. Further development of this would include the integration of holistic assessment tools which could highlight the needs of the patient, in addition to determining prognosis. The Integrated Palliative Outcome Score (IPOS) has been shown in other chronic disease groups[63] to both be able to assess patients' needs and predict mortality. However, this aspect is beyond the scope of this systematic review.

As the global increase in recognition of the importance of frailty in end-stage liver disease rises, so too does the exploration of the utility of this. As we have demonstrated, identifying frailty in this group of patients who are not eligible for transplant is important for anticipatory care planning, identifying symptoms and considering referral to specialist palliative care; however, it also may be a trigger for considering intervention. This could be communicated with primary or secondary care physicians when it is found that a patient is frail and ineligible for transplant or could indeed be incorporated into routine hepatology clinic practice and used as a way of identifying trajectory associated with frailty in this group. Across the spectrum of management options for end-stage liver disease, there is expert consensus that further research into therapeutic and multimodal strategies for targeting frailty is urgently needed.[64]

5 | STRENGTHS AND LIMITATIONS

Much of the previously published work on the use of frailty assessment in patients with cirrhosis has focussed on a pure transplant setting.[24,25,54] These studies feature only a self-selecting patient cohort with advanced liver disease given they may be considered fit enough to consider an orthotopic liver transplant. Our review presents the first summary of frailty assessment in patients without a focus on transplant. Due to the small numbers of transplants performed each year, we hypothesise that within our included populations, the vast majority will not receive transplants, however, it is impossible to extrapolate this fully given the inherent limitations within the studies themselves. We identified some comparative studies of reasonable quality which contrasted different frailty assessments in the same patient populations, thus allowing for a critique of the different indices.

Some studies ($n = 4$) were excluded due to being unable to distinguish between transplanted vs non-transplanted patients or due to studies only reporting transplant-free survival. Being unable to distinguish those who were transplanted or died pre-transplant or were not suitable for transplant would have been beneficial to examine differences in frailty in these groups; however, the design of those excluded studies meant this key variance could not be explored. Indeed, a further 60 studies were excluded as these focussed only on a transplant setting—highlighting that current research is heavily directed to end-stage cirrhosis which has a relative bias toward only exploring transplant-related areas.

6 | CONCLUSION

This review has presented a breadth of different frailty assessors which all can predict mortality, to varying degrees, though they have only been studied in a limited format. Further work is needed before a consensus can be reached on the best method of frailty assessment. Indeed, there is likely an argument for utilising different methods of frailty assessment dependent on the patient, setting and available resources. Shifting the focus from transplant to the more realistic view of supportive liver care is paramount to ensuring appropriate anticipatory care planning and symptom control can be implemented early. The inclusion of a frailty assessment into routine clinical practice has benefits reaching beyond suitability for transplant and can help facilitate such conversations around prognosis and development of holistic patient-focussed future care planning.

AUTHOR CONTRIBUTIONS

Sarah P Bowers: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Paul N Brennan:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **John F Dillon:** Conceptualization (equal); supervision (lead); writing – review and editing (lead).

ACKNOWLEDGEMENT

Declaration of personal interests: None.

FUNDING INFORMATION

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors relating to this work. PNB has received educational honoraria from Takeda. JFD has received research grants and lecture honoraria from MSD, Abbvie and Gilead.

AUTHORSHIP

Guarantor of the article: Sarah P. Bowers.

ORCID

Sarah P. Bowers https://orcid.org/0000-0003-0722-8318

TWITTER

Sarah P. Bowers @SarahPBowers
Paul N. Brennan @brennap9
John F. Dillon @profjohndillon

REFERENCES

1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151–71.
2. Gov.uk. Liver disease: applying All Our Health. 2020 23/03/2020.
3. Trust BL. The alarming impact of liver disease in the UK. June 2019.
4. Janani K, Jain M, Vargese J, Srinivasan V, Harika K, Michael T, et al. Health-related quality of life in liver cirrhosis patients using SF-36 and CLDQ questionnaires. Clin Exp Hepatol. 2018;4(4):232–9.
5. Orr JG, Homer T, Ternent L, Newton J, McNeil CJ, Hudson M, et al. Health related quality of life in people with advanced chronic liver disease. J Hepatol. 2014;61(5):1158–65.
6. Younossi Z, Henry L. Overall health-related quality of life in patients with end-stage liver disease. Clin Liver Dis (Hoboken). 2015;6(1):9–14.
7. Transplant NBa. Annual report on Liver Transplant 2021 September 2021.
8. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1–85.
9. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646–9.
10. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.
11. Peng Y, Qi X, Guo X. Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Medicine (Baltimore). 2016;95(8):e2877.
12. Kok B, Abraldes JG. Child-Pugh classification: time to abandon? Semin Liver Dis. 2019;39(1):96–103.
13. Bedreli S, Sowa JP, Gerken G, Saner FH, Canbay A. Management of acute-on-chronic liver failure: rotational thromboelastometry may reduce substitution of coagulation factors in liver cirrhosis. Gut. 2016;65(2):357–8.
14. Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for end-stage liver disease (MELD) based on selection of clinical laboratory. Am JTransplant. 2007;7(6):1624–8.
15. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol 2005;42 (Suppl. 1):S100-7.
16. Chen SH, Wan QS, Wang T, Zhang KH. Fluid biomarkers for predicting the prognosis of liver cirrhosis. Biomed Res Int. 2020;2020:7170457.
17. Rasmussen DN, Thiele M, Johansen S, Kjærgaard M, Lindvig KP, Israelsen M, et al. Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease. J Hepatol. 2021;75(5):1017–25.
18. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44(1):217–31.
19. Bortz WM 2nd. The physics of frailty. J Am Geriatr Soc. 1993;41(9):1004–8.
20. Hamerman D. Toward an understanding of frailty. Ann Intern Med. 1999;130(11):945–50.
21. Spiers GF, Kunonga TP, Hall A, Beyer F, Boulton E, Parker S, et al. Measuring frailty in younger populations: a rapid review of evidence. BMJ Open. 2021;11(3):e047051.
22. Laube R, Wang H, Park L, Heyman JK, Vidot H, Majumdar A, et al. Frailty in advanced liver disease. Liver Int. 2018;38(12):2117–28.
23. Fried LP, Xue QL, Cappola AR, Ferrucci L, Chaves P, Varadhan R, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A Biol Sci Med Sci. 2009;64(10):1049–57.
24. Tapper EB. Frailty and outcomes after liver transplantation. Curr Transplant Rep. 2019;6(1):1–6.
25. Sinclair M, Poltavskiy E, Dodge JL, Lai JC. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. World J Gastroenterol. 2017;23(5):899–905.
26. Dunn MA, Josbeno DA, Tevar AD, Rachakonda V, Ganesh SR, Schmotzer AR, et al. Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospitalization. Am J Gastroenterol. 2016;111(12):1768–75.
27. Woodland H, Hudson B, Forbes K, McCune A, Wright M. Palliative care in liver disease: what does good look like? Frontline Gastroenterol. 2020;11(3):218–27.
28. Saab S, Ibrahim AB, Shpaner A, Younossi ZM, Lee C, Durazo F, et al. MELD fails to measure quality of life in liver transplant candidates. Liver Transplant. 2005;11(2):218–23.
29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178–89.
30. Bowers SP BPN, Dillon J.F. PROSPERO2020. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021246932.
31. National Heart LaBI. Study quality assessment tools 2021. Updated July 2021. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
32. Essam Behiry M, Mogawer S, Yamany A, Rakha M, Awad R, Emad N, et al. Ability of the short physical performance battery frailty index to predict mortality and hospital readmission in patients with liver cirrhosis. Int J Hepatol. 2019;2019:8092865.
33. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017;66(2):564–74.
34. Skladany L, Drotarova Z, Vnencakova J, Jancekova D, Molcan P, Koller T. Applicability and prognostic value of frailty assessment tools among hospitalized patients with advanced chronic liver disease. Croat Med J. 2021;62(1):8–16.
35. Singh S, Taneja S, Tandon P, Bansal A, Gorsi U, Roy A, et al. A comparison of different frailty scores and impact of frailty on outcome in patients with cirrhosis. J Clin Exp Hepatol. 2022;12(2):398–408.
36. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, 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(2):M85–94.
37. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant. 2014;14(8):1870–9.
38. Functional outcomes for clinical trials in frail older persons: time to be moving. J Gerontol Series A: Biol Sci Med Sci. 2008;63(2):160–4.
39. Wang X, Feng H, Hui Y, Zhao T, Mao L, Fan X, et al. Combining gait speed in a nomogram to predict mortality and its association with other domains of general frailty in cirrhosis. J Dig Dis. 2020;21(Suppl. 1):124.
40. Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Lai M. Standard assessments of frailty are validated predictors of mortality in hospitalized patients with cirrhosis. Hepatology. 2015;62(2):584–90.
41. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, 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 (London, England). 2018;391(10132):1775–82.
42. Shah S, Goldberg DS, Kaplan DE, Sundaram V, Taddei TH, Mahmud N. Patient frailty is independently associated with the risk of hospitalization for acute-on-chronic liver failure. Liver Transplant. 2021;27(1):16–26.
43. McAlister FA, Lin M, Bakal JA. Prevalence and Postdischarge outcomes associated with frailty in medical inpatients: impact of different frailty definitions. J Hosp Med. 2019;14(7):407–10.
44. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. Canadian Med Assoc J. 2005;173(5):489–95.
45. Tandon P, Tangri N, Thomas L, Zenith L, Shaikh T, Carbonneau M, et al. A rapid bedside screen to predict unplanned hospitalization and death in outpatients with cirrhosis: a prospective evaluation of the Clinical Frailty Scale. Am J Gastroenterol. 2016;111(12):1759–67.
46. Deng Y, Lin L, Hou L, Fan X, Zhao T, Mao L, et al. A self-reported Frailty Index predicts long-term mortality in hospitalized patients with cirrhosis. Ann Transl Med. 2020;8(19):1217.
47. Guerard EJ, Deal AM, Chang Y, Williams GR, Nyrop KA, Pergolotti M, et al. Frailty Index developed from a cancer-specific geriatric assessment and the association with mortality among older adults with cancer. J Nat Compr Canc Netw. 2017;15(7):894–902.
48. Orman ES, Ghabril M, Chalasani N. Poor performance status is associated with increased mortality in patients with cirrhosis. Clin Gastroenterol Hepatol. 2016;14(8):1189–95.e1.
49. Tandon P, Reddy KR, O'Leary JG, Garcia-Tsao G, Abraldes JG, Wong F, et al. A Karnofsky performance status-based score predicts death after hospital discharge in patients with cirrhosis. Hepatology. 2017;65(1):217–24.
50. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.
51. Román E, Parramón M, Flavià M, Gely C, Poca M, Gallego A, et al. Frailty in outpatients with cirrhosis: a prospective observational study. Liver Int. 2021;41(2):357–68.
52. Kremer WM, Nagel M, Reuter M, Hilscher M, Michel M, Kaps L, et al. Validation of the Clinical Frailty Scale for the prediction of mortality in patients with liver cirrhosis. Clin Transl Gastroenterol. 2020;11(7):e00211.
53. Jacob M, Copley LP, Lewsey JD, Gimson A, Rela M, van der Meulen JH. Functional status of patients before liver transplantation as a predictor of posttransplant mortality. Transplantation. 2005;80(1):52–7.
54. Lai JC, Sonnenday CJ, Tapper EB, Duarte-Rojo A, Dunn MA, Bernal W, et al. Frailty in liver transplantation: an expert opinion statement from the American Society of Transplantation liver and intestinal Community of Practice. Am J Transplant. 2019;19(7):1896–906.
55. Brustia R, Savier E, Scatton O. Physical exercise in cirrhotic patients: towards prehabilitation on waiting list for liver transplantation. A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2018;42(3):205–15.
56. Williams FR, Milliken D, Lai JC, Armstrong MJ. Assessment of the frail patient with end-stage liver disease: a practical overview of sarcopenia, physical function, and disability. Hepatol Commun. 2021;5(6):923–37.
57. Lin FP, Visina JM, Bloomer PM, Dunn MA, Josbeno DA, Zhang X, et al. Prehabilitation-driven changes in frailty metrics predict mortality in patients with advanced liver disease. Am J Gastroenterol. 2021;116(10):2105–17.
58. Croome KP, Taner CB. The changing landscapes in DCD liver transplantation. Curr Transplant Rep. 2020;7(3):194–204.
59. Hamaker ME, van den Bos F, Rostoft S. Frailty and palliative care. BMJ Support Palliat Care. 2020;10(3):262–4.
60. Stow D, Spiers G, Matthews FE, Hanratty B. What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. Palliat Med. 2019;33(4):399–414.
61. Low J, Vickerstaff V, Davis S, Bichard J, Greenslade L, Hopkins K, et al. Palliative care for cirrhosis: a UK survey of health professionals' perceptions, current practice and future needs. Frontline Gastroenterol. 2016;7(1):4–9.
62. Poonja Z, Brisebois A, van Zanten SV, Tandon P, Meeberg G, Karvellas CJ. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol. 2014;12(4):692–8.
63. Sexton DJ, Lowney AC, O'Seaghdha CM, Murphy M, O'Brien T, Casserly LF, et al. Do patient-reported measures of symptoms and health status predict mortality in hemodialysis? An assessment of POS-S renal and EQ-5D. Hemodial Int. 2016;20(4):618–30.
64. Lai JC, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, 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(3):1611–44.

How to cite this article: Bowers SP, Brennan PN, Dillon JF. Systematic review: the role of frailty in advanced chronic liver disease. Aliment Pharmacol Ther. 2022;00:1–10. https://doi.org/10.1111/apt.17324