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ORIGINAL ARTICLE

Prospective Study

Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist

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Abstract

AIM

To investigate the impact of physical frailty on risk of hospitalisation in cirrhotic patients on the liver transplant waitlist.

METHODS

Cirrhotics listed for liver transplantation at a single centre underwent frailty assessments using the Fried Frailty Index, consisting of grip strength, gait speed, exhaustion, weight loss, and physical activity. Clinical and biochemical data including MELD score as collected at the time of assessment. The primary outcome was number of hospitalised days per year; secondary outcomes included incidence of infection. Univariable and multivariable analysis was performed using negative binomial regression to associate baseline parameters including frailty with clinical outcomes and estimated incidence rate ratios (IRR).

RESULTS

Of 587 cirrhotics, 64% were male, median age (interquartile range) was 60 (53-64) years and MELD score was 15 (12-18). Median Fried Frailty Index was 2 (1-3); 31.6% were classified as frail (fried frailty $\geqslant$ 3). During 12 mo of follow-up, 43% required at least 1

hospitalisation; 38% of which involved major infection. 107/184 (58%) frail and 142/399 (36%) non-frail patients were hospitalised at least once ($P < 0.001$). In univariable analysis, Fried Frailty Index was associated with total hospitalisation days per year (IRR = 1.51, 95%CI: 1.28-1.77; $P \leqslant 0.001$), which remained significant on multivariable analysis after adjustment for MELD, albumin, and gender (IRR for frailty of 1.21, 95%CI: 1.02-1.44; $P = 0.03$). Incidence of infection was not influenced by frailty.

CONCLUSION

In cirrhotics on the liver transplant waitlist, physical frailty is a significant predictor of hospitalisation and total hospitalised days per year, independent of liver disease severity.

Key words: Hospitalisation; Infection; Cirrhosis; Frailty; Transplantation

Core tip: This study demonstrates a significant independent link between bedside measures of physical frailty and risk for hospitalisation in cirrhotic patients on the liver transplant waitlist. This adds to previous data showing a link between frailty and mortality in cirrhosis, and therefore allows us to better select at-risk cirrhotic patients who are most in need of more intense chronic disease management programs.

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INTRODUCTION

The most commonly used tool to prioritise patients for liver transplantation is the MELD or MELD-sodium score[1], which fails to capture the decline in systemic health suffered by many liver transplant candidates. This is particularly relevant as liver transplant recipients are ageing and accumulating comorbidities[1]. Muscle wasting and weakness are incredibly common, observed in up to 70% of waitlisted individuals[2]. Both quantitative measures of muscle mass and functional measures of muscle strength have been associated with waitlist mortality, infection and post-transplant complications[3-5].

Frailty is a multi-system disorder that is classically associated with ageing, disability and comorbidity, and is known to increase the risk for falls, hospitalisation and mortality[6]. Quantification of frailty is most commonly performed using the Fried Frailty Index. Initially designed for use in geriatric populations, the Fried Frailty Index encompasses handgrip strength, exhaustion, gait speed, unintentional weight loss and physical activity[7]. Some data suggest that functional measures of muscle strength may better predict outcomes in cirrhotics than CT-based measures of sarcopenia[8]. Furthermore, frailty measures can be performed at the bedside, without the need for ionising radiation, which makes them preferable for repeated measures to assess changes over time. This is important as progression of frailty is itself associated with poorer outcome[9].

Physical frailty as measured the by Fried Frailty Index has previously been identified as a risk factor for mortality in cirrhosis[3,4], yet there are little data investigating the impact of frailty on hospitalisation in cirrhosis. An independent link between low muscle mass and infection risk has been identified pre-liver transplantation[5,10], as well as increased hospitalisation days[11], and thus similar findings may be expected for frailty.

This study aims to evaluate the impact of frailty on total number of hospitalisation days. The ultimate goal is to identify an at-risk subset of the cirrhotic population to assist in the development of preventative strategies to improve outcomes in this vulnerable population.

MATERIALS AND METHODS

We report a single-centre prospective observational cohort study of 587 pre-transplant cirrhotics, performed at the University of California, San Francisco, between July 2012 and December 2014.

Subjects

All adult ($\geqslant$ 18 years) cirrhotic subjects actively listed for liver transplantation for cirrhosis are invited to enrol in the ongoing prospective Functional Assessment in Liver Transplantation (FrAILT) study. Ninety-seven percent of invited participants enrol in this study. Enrolment occurs in the outpatient setting as described previously[3]. All patients provided written informed consent. Major exclusion criteria include inability to consent due to severe encephalopathy (numbers count > 120 s), prior transplantation due to the impact of immunosuppressants on muscle function, as well as transplant listing for reasons other than cirrhosis. Patients with incomplete frailty testing measures at baseline or lost-to-follow-up at 12 mo were also excluded.

Baseline variables

At study entry, patient demographics including age, sex, disease aetiology, and medical comorbidities (including hepatocellular carcinoma, diabetes, coronary artery disease and HIV infection) were recorded. Standard baseline biochemical parameters were retrieved from electronic medical records including liver function

tests to calculate MELD score, coagulation profile, full blood count and electrolyte profile. Clinical information regarding the presence of ascites, ascertained by the patient's primary hepatologists, was recorded. Hepatic encephalopathy was assessed using the numbers connection test, with a score > 35 s indicating the presence of encephalopathy[12].

Frailty assessments

Assessments of physical frailty were performed in the outpatient setting using the Fried Frailty Index, consisting of grip strength, gait speed, exhaustion, weight loss, and physical activity. Frail was defined as Fried Frailty Index ⩾ 3 points out of a maximum of 5. These assessments have been validated in geriatric and cirrhotic populations[3,7,9,13].

Short physical performance battery (SPPB) assessment was also undertaken as a second measure to validate findings using the Fried Frailty Index. The SPPB comprises gait speed, standing balance (ability to perform a tandem stand) and chair stands (time taken to complete 5 chair stands. Frail is defined as a SPPB score ⩽ 9. This score has also been associated with poor outcome in cirrhosis[3].

Outcomes

The primary outcome was number of hospitalised days per year during the 12 mo follow-up period immediately following the frailty assessment. This was determined from medical records at the home institution and review of external medical records in the case of hospital admissions elsewhere. Patients who died or were transplanted within 12 mo were censored at this time (n = 82).

Secondary outcomes included number of hospitalisations over 12 mo, length of stay per hospitalisation, and hospitalisation for major infection. Infection was defined according to NACSELD (North American Consortium for Studies of End-Stage Liver Disease) criteria[14], to avoid inadvertent inclusions of subjects receiving empirical antibiotic therapy for liver decompensation.

Alternate causes of hospitalisation were listed as hepatic encephalopathy, acute kidney injury, ascites, gastrointestinal bleeding or other, according to hospital discharge records.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician. Descriptive statistics are displayed as the median [interquartile range (IQR)] unless stated otherwise. Wilcoxon rank-sum and χ^2 tests compared frail *vs* non-frail and hospitalised *vs* non-hospitalised patients,

Univariable negative binomial regression evaluated the association of frailty with hospitalisation days per year and estimated incidence rate ratios (IRR) and 95%CI. Variables significant at the 0.2 level and below were included in the multivariate model. Backward elimination (P > 0.05 for removal) was used to select the final multivariable model.

Logistic regression was used to evaluate the relationship between hospitalisation for infection and frailty. Bivariable regression models estimated OR and 95%CIs for each factor while accounting for observation time. Characteristics with a bivariable P value below 0.2 were assessed in the multivariable model to allow for consideration of all possible contributing factors. Backward elimination (P > 0.05 for removal) identified the subset of variables associated with hospitalisation for infection while adjusting for observation time. Frailty (Fried Frailty Index ⩾ 3) was included in the final model as the predictor of interest.

A cut-off P value less than 0.05 was used to determine statistical significance. Analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

RESULTS

616 consecutive cirrhotic patients were enrolled into the FrAILT study between July 2012 and February 2015. 587 (95%) of these patients had complete data for analysis in this study. The median (IQR) age was 60 (53-64) years, BMI 28.2 (24.8-33.1) cm/m^2, and median MELD score was 15 (12-18) and 64.2% were male. Fifty-seven percent were Caucasian, 26% Hispanic, 7% Asian, 4% African American, and 6% were of other ethnicity. Four patients had missing Fried Frailty Index. Thirty-one point six percent of patients were classified as frail, as defined by a Fried Frailty Index of 3 or above. Frail patients had more severe liver failure than non-frail patients as measured by MELD score and features of decompensation, and lower rates of hepatocellular carcinoma. Frail patients were slightly but significantly older than non-frail patients. Baseline demographics by frailty group are described in Table 1.

Outcomes

During the 12 mo study period, 43% of subjects required at least 1 hospitalisation. The primary reason for hospitalisation was infection in 39%, hepatic encephalopathy in 19%, acute kidney injury or ascites in 16%, GI bleeding in 8% or other miscellaneous cause in 19%. In those patients requiring hospitalisation (n = 243, for eight hospitalised patients the number of hospitalisations is unknown), 54% had a single hospitalisation, 33% had 2 or 3 hospitalisations, and 13% had 4 or more hospitalisations. The median (IQR) length of stay per hospitalisation was 4.5 (3.0-7.5) d.

Risk factors for hospitalisation

Using a Fried Frailty Index of ⩾ 3, frail patients were significantly more likely to be hospitalised, with 58% of frail and 36% of non-frail patients hospitalised at least once in the subsequent 12-mo period (P <

Table 1 Baseline demographics of waitlisted cohort enrolled into the FrAILT study stratified by frail (Fried Frailty Index ≥ 3) and non-Frail (Fried Frailty Index < 3)

Characteristic	Overall (*n* = 587)	Frail (*n* = 184)	Non-frail (*n* = 399)	*P* value
Age (yr)	60 (53-64)	60 (54-64)	59 (52-63)	0.03
Male	64%	60%	66%	0.12
BMI (kg/m^2)	28 (25-33)	28 (25-33)	28 (25-33)	0.74
MELD (points)	15 (12-18)	16 (14-20)	14 (12-17)	< 0.001
Albumin (g/dL)	3.0 (2.6-3.5)	2.9 (2.5-3.2)	3.2 (2.7-3.6)	< 0.001
Sodium (nmol/L)	137 (134-139)	135 (132-138)	137 (135-139)	< 0.001
HCC	33%	25%	36%	0.004
Numbers connection test (s)	40 (30-54)	46 (34-61)	38 (29-51)	< 0.001
Ascites	28%	40%	22%	< 0.001
HIV	2.9%	2.7%	3.0%	0.85
Diabetes	31%	32%	30%	0.46

BMI: Body mass index; MELD: Model for end stage liver disease; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus.

Table 2 Significant differences between patients hospitalised within 12 mo and non-hospitalised individuals

Characteristic	Hospitalised, *n* = 251	Non-hospitalised, *n* = 336	*P* value
Age (yr)	59 (53; 63)	60 (55; 64)	0.02
Male gender	57%	69%	0.003
MELD score	16 (13; 20)	14 (11; 17)	< 0.001
Albumin (g/dL)	2.8 (2.5; 3.2)	3.2 (2.8; 3.7)	< 0.001
Sodium (mmol/L)	136 (133; 139)	137 (135; 139)	0.002
Fried Frailty Index	2 (1; 3)	2 (1; 2)	< 0.001
SPPB score	11 (9; 12)	11 (10; 12)	< 0.001
Chair stands per second	0.4 (0.3-0.5)	0.5 (0.4-0.6)	< 0.001
Walk speed (m/s)	1.2 (0.9-1.4)	1.3 (1.1-1.6)	< 0.001
Handgrip strength (kg)	27.7 (21.7; 35.3)	32.7 (25.0; 40.9)	< 0.001
Encephalopathy (numbers connection score)	41.6 (31.7; 57.3)	38.3 (29.4; 52.1)	0.008

MELD: Model for end stage liver disease; SPPB: Short physical performance battery.

Table 3 Significant predictors of hospitalisation days per 12 mo on multivariable analysis

Characteristic	IRR (95%CI), *n* = 583	*P* value
Frail by Fried Frailty Index	1.21 (1.02, 1.44)	0.03
MELD score	1.10 (1.06, 1.15)	< 0.001
Albumin (g/L)	0.43 (0.31, 0.61)	< 0.001
Female sex	1.85 (1.22, 2.81)	0.004

Frail-Fried Frailty Index ≥ 3. IRR: Incidence rate ratios; MELD: Model for end-stage liver disease.

0.001). Frail patients had more hospitalisation [median 1 hospitalisation (0-2) *vs* 0 hospitalisations (0-1), *P* < 0.001] and spent more days in hospital than non-frail patients [median 3 (0-8.2) d *vs* 0 (0-4) d, *P* < 0.001].

The significant differences between patients who were hospitalised compared with not hospitalised within 12 mo are displayed in Table 2. Walk speed was slower (median 1.2 *vs* 1.3 metres/second), handgrip strength was lower (median 27.7 kg *vs* 32.7 kg) and chair stands completed per second was also lower in hospitalised patients (median 0.4 stands/s *vs* 0.5 stands/s), indicating greater frailty. Females were more likely to be hospitalised than men (51% *vs* 38%, *P* = 0.003). Subjects who were hospitalised were marginally younger than those who were non-hospitalised (median age 59 *vs* 60 years, *P* = 0.02).

Among patients with at least one hospitalisation, the median (IQR) length of stay per hospital admission was similar by frailty status [5 (3.0-8.0) d for frail *vs* 4 (3.0-6.3) d for non-frail, *P* = 0.24]. For patients hospitalised for infection, the median (IQR) length of stay was longer, at 6 (3.5-8.3) d, as compared to 3.5 (2.2-6.0) d for those hospitalised for other causes, *P* < 0.001.

On univariable analysis, the Fried Frailty Index, as a continuous variable, was associated with total hospitalisation days per year (IRR = 1.51, 95%CI: 1.28-1.77; *P* < 0.001). This remained significant on multivariable analysis after adjustment for MELD, albumin, and female sex (IRR = 1.21, 95%CI: 1.02-1.44; *P* = 0.03). Table 3 displays the significant results of the negative binomial regression model.

Risk factors for infection

Twenty percent of frail patients compared to 15% of non-frail patients experienced infection (*P* = 0.09). On bivariable analysis (incorporating time to outcome), the point estimates were suggestive of an increased odds of infection for frail *vs* non-frail patients although statistical significance was not achieved by SPPB or Fried Frailty Index (Table 4). There was however a significantly reduced odds of infection in patients who could complete 5 chair stands within 10 s (*P* = 0.046). In addition, the MELD score was significantly associated with the incidence of infection, and serum albumin and the presence of hepatocellular carcinoma were inversely associated with infection. There was no significant relationship for other factors, including the presence of ascites (OR = 1.15, *P* = 0.570), HIV infection (OR = 1.53, *P* = 0.464) or diabetes (OR = 0.98, *P* = 0.939).

On multivariable analysis, only serum albumin (OR = 0.39, 95%CI: 0.26-0.58, *P* < 0.001) and the

Table 4 Predictors of infection on bivariable analysis (accounting for observation time)

Characteristic	OR (95%CI)	*P* value
Albumin (g/dL)	0.40 (0.27-0.60)	< 0.001
MELD score	1.07 (1.02-1.11)	0.005
HCC (yes *vs* no)	0.60 (0.36-0.99)	0.046
Chair stands (completion of 5 chair stands within 10 s)	0.32 (0.11-0.98)	0.046
Age (yr)	0.98 (0.96-1.0)	0.05
Frail (SPPB score ≤ 9)	1.54 (0.94-2.50)	0.08
Frail (Fried frailty Index ≥ 3)	1.49 (0.94-2.36)	0.09
Sodium	0.96 (0.90-1.01)	0.10
Hepatic encephalopathy (numbers connection > 45 s)	0.72 (0.46-1.14)	0.16

MELD: Model for end stage liver disease; HCC: Hepatocellular carcinoma; SPPB: Short physical performance battery.

presence of hepatic encephalopathy (OR = 0.59, 95%CI: 0.36-0.95, *P* = 0.03) remained significant predictors of infection. Frailty, as measured by the Fried Frailty Index, was not significant in this model (OR = 1.30 Fried Frailty Index ≥ 3 *vs* < 3, 95%CI: 0.80-2.12, *P* = 0.29).

DISCUSSION

This prospective study, including nearly 600 patients with cirrhosis awaiting liver transplantation, demonstrates that functional measures of frailty are associated with increased hospitalisation days independent of the MELD score. The increase in hospitalisation observed in this study was due to an increased incidence of hospitalisation, predominantly for complications of end-stage liver disease. These data from the ongoing FrAILT study add critical information to our prior report on the significant association between frailty and waitlist mortality[3] by providing an intermediate outcome of hospitalisation. The clinical implication of this finding is that functional frailty measures performed in the outpatient setting can identify patients who may benefit from tailored interventions to reduce the risk of subsequent hospitalisations and ultimately, death.

Our data have important implications for the management of patients with cirrhosis, who impose a high burden on the health care system with frequent exacerbations of their chronic disease. In particular, implementation of a chronic disease model of care for decompensated cirrhotics has strong potential to improve outcomes in this population[15]. Indeed, in one study in Italy, case management was shown to significantly reduce both the 30 d re-hospitalisation rate as well as overall mortality, while reducing cost[16]. Given the resource requirements of such a program it is not practical or feasible to suggest that every cirrhotic should be enrolled, therefore a simple frailty measure such as the Fried Frailty Index is useful in its ability to select patients who are most in need of such an intensive management strategy. Perhaps even more importantly, frailty represents a potentially modifiable outcome through focused pre-habilitation programs that specifically target the individual components that contribute to the frail phenotype[17]. Demonstrating that frailty is associated with increased hospitalisations provides strong justification to develop and implement such programs early in the disease progression to prevent hospitalisation and subsequent deterioration in this vulnerable population.

In our cohort, frailty was not significantly associated with infection on multivariable analysis, although there was a trend to increased infection. This differs from previous research demonstrating that sarcopenia, a major contributor to the frail phenotype, has previously been shown to increase risk of infection-related hospitalisations[10]. It may be that frailty represents an early phenotype, whereas sarcopenia represents more established systemic disturbance that may be required for infection risk. However in the absence of longitudinal data incorporating frailty measures and body composition measurements, this cannot be confirmed. It may also be that quantification of hepatic encephalopathy in this cohort by the numbers count test, a feature recognised to be closely related to frailty[18], allowed us to better ascertain the relative contributions of different factors to infection risk than previous studies. The lack of an independent association between frailty and infection was somewhat surprising, and further studies are required to clarify this issue.

The majority of hospital admissions in our cohort were indeed for liver-related decompensation including infection, but also acute kidney injury, hepatic encephalopathy and hepatorenal syndrome (81%), and thus could be expected to accelerate the progression of liver disease. This sheds important insight into the potential mechanisms of the impact of frailty on adverse health outcomes in cirrhotics: instead of increasing the likelihood of any single complication, frailty decreases a patient's reserve to withstand any of the typical complications of cirrhosis, increasing the severity of the complications and the likelihood of inpatient admission.

Limitations of this study include its observational nature, albeit prospective, therefore the impact of reversing frailty cannot be proven. However the consistent associations between frailty and poor outcome suggest that it is indeed itself a contributing factor, and the finding that deterioration in frailty further increases risk of mortality adds further weight to this argument[9]. Furthermore, data from a study of patients undergoing TIPS insertion suggest that reversing muscle wasting can indeed improve survival[19]. An additional limitation is the inability to accurately classify the cause for non-infectious hospital admissions in this study, to determine whether the increase in hospitalisation was due to a specific factor, such as hepatic encephalopathy. Most episodes of decompensation of liver disease are multifactorial in nature, the specific triggering factor may never be identified, and standardised diagnostic

criteria are lacking. Finally, this study was single-centre, and thus validation in other cohorts is required.

Strengths of this study include a large study population that is representative of transplant waitlist cohorts with a high study uptake of 97% of patients assessed for transplantation, with near-complete (95%) longitudinal data. We therefore believe that these results are representative of a tertiary centre transplant waitlist. Despite the study limitations, our identification of a relationship between frailty - as measured by a simple tool that can easily and rapidly be performed in the clinic setting - a significantly increased risk of hospitalisation has important implications for the management of patients with cirrhosis. The Fried Frailty Index can help clinicians identify those at greatest risk of hospitalisation and thus in greatest need of chronic liver disease management programs to provide additional support.

In conclusion, physical frailty in subjects on the liver transplant waitlist, as measured by the Fried Frailty Index, is a significant predictor of 12 mo hospitalisation days independent of liver disease severity. This findings adds to the previously established link between frailty and mortality. These data provide us with a strong rationale to develop pre-habilitation and chronic disease management programs for frail patients on the transplant waitlist to reduce hospitalisation, reduce mortality and reduce healthcare costs.

COMMENTS

Background

Frailty has previously been associated with mortality in patients on the liver transplant waitlist. Its impact on hospitalisation however is no well described.

Research frontiers

As the liver transplant population is ageing and accumulating comorbidities, exploring the impact of systemic health by using measures such as the Fried Frailty Score, the authors are starting to better understand the impact of non-liver disease severity on outcome in this population.

Innovations and breakthroughs

This manuscript for the first time evaluates the impact of the Fried Frailty Score on hospitalisation days over a 12 mo period in subjects on the liver transplant waitlist. It identifies physical frailty as an independent predictor of hospitalisation risk regardless of MELD score. This adds to previous work linking frailty to mortality in cirrhosis, and is similar to previous findings relating to sarcopenia in cirrhosis, as measured by computerised tomography. Sarcopenia however has been linked with an increase in infection risk in cirrhosis, whereas in our study frailty was not significantly associated with infection.

Applications

This study provides a strong rationale to consider physical frailty as a measure of disease severity in cirrhotics on the liver transplant waitlist, and to consider prehabilitation or chronic disease management programs to minimise risk for frail cirrhotics.

Terminology

The Fried Frailty Score consists of handgrip strength, gait speed, exhaustion, weight loss, and physical activity. The score ranges from 0 to 5, with 0 being normal. Frail is generally defined as Fried Frailty Index $\geqslant$ 3 points out of a maximum of 5. These assessments have been validated in geriatric and cirrhotic populations.

Peer-review

The study is interesting because authors found that frailty is an independent factor (independent from MELD most importantly) for hospitalisation. Future results of this prospective may show that frailty might be a contributing factor for listing of transplantation priority.

REFERENCES

1 **Su F**, Yu L, Berry K, Liou IW, Landis CS, Rayhill SC, Reyes JD, Ioannou GN. Aging of Liver Transplant Registrants and Recipients: Trends and Impact on Waitlist Outcomes, Post-Transplantation Outcomes, and Transplant-Related Survival Benefit. *Gastroenterology* 2016; **150**: 441-453.e6; quiz e16 [PMID: 26522262 DOI: 10.1053/j.gastro.2015.10.043]

2 **Sinclair M**, Gow PJ, Grossmann M, Angus PW. Review article: sarcopenia in cirrhosis--aetiology, implications and potential therapeutic interventions. *Aliment Pharmacol Ther* 2016; **43**: 765-777 [PMID: 26847265 DOI: 10.1111/apt.13549]

3 **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**: 1870-1879 [PMID: 24935609 DOI: 10.1111/ajt.12762]

4 **Carey EJ**, Steidley DE, Aqel BA, Byrne TJ, Mekeel KL, Rakela J, Vargas HE, Douglas DD. Six-minute walk distance predicts mortality in liver transplant candidates. *Liver Transpl* 2010; **16**: 1373-1378 [PMID: 21117246 DOI: 10.1002/lt.22167]

5 **Montano-Loza AJ**, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, Sawyer MB. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012; **10**: 166-173, 173.e1 [PMID: 21893129 DOI: 10.1016/j.cgh.2011.08.028]

6 **Xue QL**. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011; **27**: 1-15 [PMID: 21093718 DOI: 10.1016/j.cger.2010.08.009]

7 **Fried LP**, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research G. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M146-M156 [PMID: 11253156]

8 **Wang CW**, Feng S, Covinsky KE, Hayssen H, Zhou LQ, Yeh BM, Lai JC. A Comparison of Muscle Function, Mass, and Quality in Liver Transplant Candidates: Results From the Functional Assessment in Liver Transplantation Study. *Transplantation* 2016; **100**: 1692-1698 [PMID: 27314169 DOI: 10.1097/TP.0000000000001232]

9 **Lai JC**, Dodge JL, Sen S, Covinsky K, Feng S. Functional decline in patients with cirrhosis awaiting liver transplantation: Results from the functional assessment in liver transplantation (FrAILT) study. *Hepatology* 2016; **63**: 574-580 [PMID: 26517301 DOI: 10.1002/hep.28316]

10 **Krell RW**, Kaul DR, Martin AR, Englesbe MJ, Sonnenday CJ, Cai S, Malani PN. Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. *Liver Transpl* 2013; **19**: 1396-1402 [PMID: 24151041 DOI: 10.1002/lt.23752]

11 **Montano-Loza AJ**, Meza-Junco J, Baracos VE, Prado CM, Ma M, Meeberg G, Beaumont C, Tandon P, Esfandiari N, Sawyer MB, Kneteman N. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. *Liver Transpl* 2014; **20**: 640-648 [PMID: 24678005 DOI: 10.1002/lt.23863]

12 **Weissenborn K**, Rückert N, Hecker H, Manns MP. The number connection tests A and B: interindividual variability and use for the assessment of early hepatic encephalopathy. *J Hepatol* 1998; **28**: 646-653 [PMID: 9566834]

13 **Makary MA**, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, Takenaga R, Devgan L, Holzmueller CG, Tian J, Fried LP. Frailty as a predictor of surgical outcomes in older patients. *J Am*

Coll Surg 2010; **210**: 901-908 [PMID: 20510798 DOI: 10.1016/j.jamcollsurg.2010.01.028]

14 **Bajaj JS**, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, Brown G, Noble NA, Thacker LR, Kamath PS. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology* 2012; **56**: 2328-2335 [PMID: 22806618 DOI: 10.1002/hep.25947]

15 **Volk ML**. Identifying cirrhosis patients for intensive disease management. *Dig Dis Sci* 2014; **59**: 22-23 [PMID: 24323181 DOI: 10.1007/s10620-013-2968-3]

16 **Morando F**, Maresio G, Piano S, Fasolato S, Cavallin M, Romano A, Rosi S, Gola E, Frigo AC, Stanco M, Destro C, Rupolo G, Mantoan D, Gatta A, Angeli P. How to improve care in outpatients with cirrhosis and ascites: a new model of care coordination by consultant hepatologists. *J Hepatol* 2013; **59**: 257-264 [PMID: 23523582 DOI: 10.1016/j.jhep.2013.03.010]

17 **Lai JC**, Volk ML, Strasburg D, Alexander N. Performance-Based Measures Associate With Frailty in Patients With End-Stage Liver Disease. *Transplantation* 2016; **100**: 2656-2660 [PMID: 27495749 DOI: 10.1097/TP.0000000000001433]

18 **Merli M**, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, Lattanzi B, Riggio O. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. *Metab Brain Dis* 2013; **28**: 281-284 [PMID: 23224378 DOI: 10.1007/s11011-012-9365-z]

19 **Tsien C**, Shah SN, McCullough AJ, Dasarathy S. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. *Eur J Gastroenterol Hepatol* 2013; **25**: 85-93 [PMID: 23011041 DOI: 10.1097/MEG.0b013e328359a759]

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