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Original Article

Assessment of frailty in Liver Cirrhosis: A Western Indian Experience

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ABSTRACT

Background & Aim: Frailty is a major prognostic factor in cirrhosis. Its assessment and intervention towards performance enhancement is important in the management of cirrhosis. Our study aimed to assess the prevalence of frailty in patients with cirrhosis and comparison of frailty by different indices.

Methods: One hundred and twenty cirrhotic patients were included. Frailty assessment was done using compares Fried frailty index (FFI), Clinical frailty index (CFI), Short physical performance battery (SPPB), Edmonton frail scale (EFS), Liver Frailty Index (LFI), ECOG, Karnofsky performance scale (KPS), and Instrumental activity of daily living (IADL). Risk factors of frailty analysis were made based on LFI.

Results: Mean age of presentation was 43.57±10.16years, and 80% were males. Most common etiology was alcohol (50.1%). Prevalence of frailty based on LFI, FFI, CFI, SPPB, EFS, ECOG, KPS, and IADL was 45%, 38.3%, 39.2%, 46.7%, 45%, 36.7%, 36.7%, and 29.2%. There was a significant positive association of frailty based on the LFI score with other scores (P<0.0001). Risk factors for frailty were being underweight (50% vs. 15%; P<0.0001), severity of ascites (P<0.0001), CTP score (P<0.0001), Mean MELD score (18.33±4.33 vs. 14.37±3.49; P<0.001) and MELD Na (20.43±4.62 vs. 15.50±3.95; P<0.001) was significantly higher among frails compared to non-frail patients.

Conclusions: Frailty is quite prevalent in liver cirrhosis. Frailty assessment should be routinely carried out. Frailty assessment by any score can be used to prevent further complications in these patients.

Key Words: *Cirrhosis; Frailty; Liver Frailty Index; Child-Turcotte-Pugh (CTP); Model for End-stage Liver Disease (MELD)*

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INTRODUCTION

Frailty has been defined as a "Loss of functional, cognitive, and physiologic reserve leading to a vulnerable state." Frailty may be considered a form of a nutrition-related disorder [1]. Higher incidence of frailty is seen with adding age and leads to severe adverse issues including short life span, poor quality of life, and falls that may increase the threat of disability, institutionalization, and hospitalization.

Frailty is common in patients with cirrhosis and is animportant predictor of mortality [2]. One recent multicenter study set up frailty to be present in 25% of outpatient cases [3]. It's indeed more common among rehabilitatedcases [4]. The pathogenesis of frailty is multifactorial and includes hepatic dysfunction, as well as malnutrition, low physical exertion position (both of which may be aggravated by intermittent hospitalization), systemic inflammation, and hypogonadism with resultant sarcopenia [5]. Frailty results in an overall reduced functional capacity and reserve. Frailty contributes to mortality independent of hepatic decompensation [3].

Cases with alcohol-associated liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) have an advanced frequency of sarcopenia [6]. Patients with ALD are at increased threat for malnutrition and have poorer functional status at the time of listing [7, 8]. In addition, co-morbidities like a metabolic or cardiovascular disease that are more common in some cirrhosis etiologies may also contribute to differences in frailty.

Several studies have reported that frailty increased the threat of hospitalization [9], waiting list drop-out [10], and mortality [11], and dropped the likelihood of liver transplantation (LT) [12]. Frailty assessment tools in these cases have been recently reviewed by the American Society of Transplantation Liver and Intestinal Community of Practice [13].

According to the report, it is not clear how these tools perform among convalescents. Rehabilitated cases frequently present with a flash worsening of their physical performance, therefore frailty status on admission might underrate their true physiological reserve. In addition, several measures of physiological function have limited connection for bed-bound patients. Hospitalization for an ACLD complication, still, represents an opportunity for early intervention. Management decisions in these patients largely depend on the estimated prognosis and the felicity for LT.

Our primary endpoint is to study the prevalence of frailty in patients with liver cirrhosis. Further, secondary endpoints are to compare the prevalence of frailty by different indices and to determine the factor affecting the frailty in patients with liver cirrhosis.

METHODOLOGY

This prospective study included outpatients and in-patients diagnosed with liver cirrhosis and getting treatment at our tertiary care center between March 2021 and December 2022.

All patients with cirrhosis age between 18 – 60 years, who attended the inpatients & outpatient liver clinic and were willing to participate in the study were eligible for inclusion. The exclusion criteria were failure to provide informed consent, hepatocellular carcinoma (HCC) or other active neoplastic disease with less than 6 month of survival, MELD score more than 25, previous liver transplant, overt HE at the time of testing, end-stage renal disease, pregnancy, history of recent (<6 weeks) use of drugsaffecting psychometric performances that could influence performance in frailty testing, BMI >30 Kg/m^2, any primary muscular disease.

Definitions:

Cirrhosis was defined by characteristic clinical (ascites, upper GI bleeding, hepatic encephalopathy, caput medusae, spider naevi, etc.), laboratory, and radiological findings (typical morphological changes of the liver, signs of portal hypertension, etc. in ultrasonography or computed tomography scanning), or via histology [14].

Compensated and a decompensated state based on the absence or the presence of any of bleeding, ascites, encephalopathy, or jaundice, respectively [15].

The study was performed after approval from the institutional ethics committee. The patients fulfilling the inclusion criteria were given information about the nature and purpose of the study.

Regarding the severity of liver disease, the patients were classified into three groups according to the Child Pugh score [16], as followed: Class A, Class B and Class C. We also classified the cases in the subgroup based on etiology, socioeconomic status, BMI, Ascites, MELD and MELD-Na score. Socio-economic status (SES) was determined by using Modified Kuppuswamy scale [17]. The body mass index (BMI) and corrected BMI [18] was calculated using Quetelet index. Asian classification of obesity [19] was used. Ascites was graded into mild, moderate & severe according to the amount of fluid in the abdominal cavity [20]. Complete blood count, Biochemical liver function tests, serum calcium and in-organic phosphate levels were measured by automated procedures.

Frailty assessment

The prevalence and characteristics of frailty was determined using Liver frailty index (LFI) [21, 22], Fried frailty criteria (FFC) [23], Clinical Frailty Index (CFI) [24], Short Physical Performance Battery (SPPB) [25], Edmonton frail scale [26], Karnofsky performance Scale [27], Instrumental activity of daily living (IADL) [28] and Eastern Cooperative Oncology Group Performance scale (ECOG PS) [29] in patients with cirrhosis.

Liver Frailty Index (LFI) [21]

The LFI includes handgrip strength, chair stand test, and balance testing.A patient is said to be frail if LFI >4.5, prefrail if 3.2–4.5, and robust if LFI<3.2. The LFI was calculated in all patients at the start of the study using an online calculator available at http://liverfrailtyindex.ucsf.edu [22].

Fried frailty criteria [23]

Fried frailty index has five criteria, more than and equal to three should be present to label the patient as being frail. If less than three are presents, then the patient is labelled as being pre-frail (Supplementary Table S1)

CLINICAL FRAGILITY INDEX [24]

Clinical fragility index is a questionnaire-based scale. It includes nine questions to label patients from very fit to terminally ill (Supplementary Table S2).

SHORT PHYSICAL PERFORMANCE BATTERY (SPPB) [25]

The short physical performance battery (SPPB) is a group of tests that combines the results of the gait speed, chair stand and balance tests. It has been used as a predictive tool for possible disability. The scores range from 0 (worst performance) to 12 (best performance).

EDMONTON FRAIL INDEX [26]

Edmonton frail index which is also a questionnaire-based scale to diagnosed frailty in subjects. 0-5 = non-Frail, 6-7 Vulnerable, 8-9 – Mild, 10-11 – Moderate, 12-17 – Severe (Supplementary Table S3).

KARNOFSKY PERFORMANCE SCALE (KPS) [27]

The Karnofsky Performance Scale (KPS) is also a questionnaire-based assessment tool for functional impairment. It is used to improve understanding of patient needs, ability to carry out daily activities and to assess patient prognosis (Supplementary Table S4).

INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (IADL) [28]

The Instrumental Activities of Daily Living Scale (IADL) is an appropriate instrument to assess independent living skills. There are eight domains of function measured with the IADL scale. Women are scored on all 8 areas of function; historically, for men, the areas of food preparation, housekeeping, laundering are excluded. Clients are scored according to their highest level of functioning in that category. A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women, and 0 through 5 for men (Supplementary Table S5).

ECOG PERFORMANCE SCALE [29]

ECOG performance status represents an assessment of a patient's level of functioning in terms of self-care, daily activity, and physical ability, it can be compared with the ADL and IADL scales. The ECOG scale directly provides one score according to general descriptions of patient performance status. ECOG performance status is assessed by physicians, while the ADL and IADL scales are questionnaires filled out by patients. ECOG score of ≥ 2 is used to define frailty [29].

STATISTICAL ANALYSIS

Data were recorded on case proforma, and entered Microsoft® Excel worksheet 2007, and exported into SPSS v21.0 (IBM, USA) for statistical analysis. Categorical variables were expressed as frequency and percentage and compared using the Chi-square test with or without Yate's correction. Normality of data was determined using Shapiro-Wilk test. Normally distributed variables were compared between two groups using independent t-test. Non-normative data were compared using Mann Whitney U test. P value <0.05 was considered statistically significant.

RESULTS:

Baseline characteristics

One hundred fifty-two patient cirrhotic patients were screened for this study, out of which 32 patients were excluded. We included total 120 cirrhotic patient, as shown in Figure 1.

We observed that mean age of the patients was 43.57 years (43.57±10.16). Male to female ratio was 4:1. Forty-four (36.7%) were from Lower-middle class.Thirty-seven (30.8%) were underweight. The most common co-morbidity was hypertension (n-24, 20%). Alcohol was the most common cause of cirrhosis (n=62, 57.7%) followed by viral (n=37, 30.8%).

Based on LFI, 45% of cirrhotic patients were frail. We observed that the frailty rates were comparable in terms of age, gender distribution and socioeconomic status. However, rate of frailty was significantly higher among underweight patients (P=0.001) (Table 1).

Our study observed that frail patients had a significantly lower level of hemoglobin (P=0.008), total protein (P=0.005), albumin (P=0.003), higher WBCs (P=0.007) and higher total bilirubin (P<0.0001) compared to the patients who were not frail (Table 2).

Seventy (58%) patients had ascites (Mild, Moderate & Severe were 23 (32.8%), 29 (41.4%) & 18 (25.7%)). Severe ascites was significantly associated with frailty (P<0.0001). Forty-six (38.3%) patients had hematemesis on presentation however it was not significantly associated with presence of frailty (P=0.076). Frail patients have significantly higher MELD and MELD-Na compared withnon-frail patients (P<0.0001). 4 (3.3%), 20 (16.6%) & 30 (25%) were frail in CTP-A, CTP-B & CTP-C group respectively. CTP Score was significantly associated with frailty (Table 3).

Prevalence of frailty based on LFI, FFI, CFI, SPPB, EFS, ECOG, KPS, and IADL was 45%, 38.3%, 39.2%, 46.7%, 45%, 36.7%, 36.7%, and 29.2%. Rate of frailty by Liver frailty index were comparable with other scales (P<0.0001) (Table 4).

DISCUSSION

This is one of the few studies in India that revealed frailty in the patients with cirrhosis of liver. Our study showed a higher prevalence of frailty (45%) in liver cirrhosis based on LFI. Recently, Singh et al reported that 43.1% of their cirrhotic patients were frail [30].

Cron and coworkers from the western world showed the prevalence of frailty in cirrhotic were 43.2% that was comparable to our study [31]. But from other study, 18% outpatients were frail [32]. That depends on the population evaluated, the methods of assessment, and the operational definitions used. Higher prevalence of frailty could be due to the low socio-economic status, poor nutrition, and late referral of patients to the hospital in developing countries compared to the West [30].

However, in our study, except BMI, none of the demographic characteristics was significantly associated with frailty. In our study, there were a significantly higher population of underweight patients compared with non-frail patients. Frailty is most often defined as having at least three of the following risk factors: unintentional weight loss, fatigue or exercise intolerance, weakness, slowed motor performance, and low physical activity. Frailty is found to be associated with muscle, strength, and weight loss [33].

In our study, severely of ascites, higher CTP score and Meld scores were significantly associated with frailty. These findings are in concordance with Singh et al. [15] However, Bhanji et al did not report any significant difference of CTP and MELD score between frail and non-frail patients. Lai and Colleague reported that the odds of frailty were higher for patients with ascites (adjusted odd ratio, 1.56; 95% CI, 1.15–2.14) [3].

We acknowledge the following limitations to our study. First, we could not evaluate if frailty could be associated with increased length of hospitalization and mortality. Second, we used LFI in our study and different frailty items may contribute differently to outcomes. Despite these limitations, the findings from this study are consistent with previous work.

CONCLUSION

Frailty exhibits a notable prevalence among individuals with liver cirrhosis. Contributing risk factors encompass being underweight, ascites severity, CTP score, MELD score, and MELD Na. The evaluation of frailty using various indices, including the Fried Frailty Index (FFI), Clinical Frailty Index (CFI), Short Physical Performance Battery (SPPB), Edmonton Frail Scale (EFS), Liver Frailty Index (LFI), ECOG, Karnofsky Performance Scale (KPS), and Instrumental Activity of Daily Living (IADL), offers valuable avenues for mitigating potential complications in these patients. This underscores the importance of early assessment and intervention to enhance patient well-being and outcomes.

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FIGURE AND TABLES

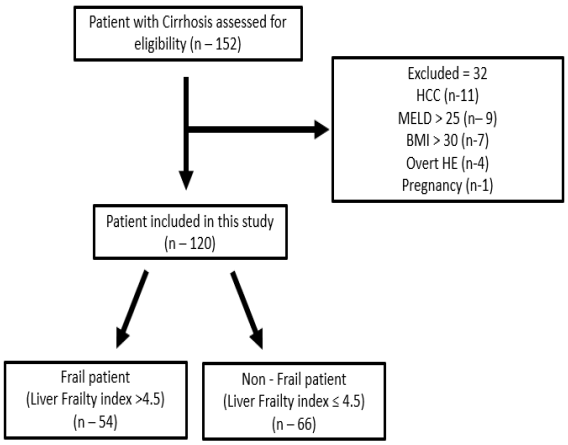

Figure 1: Flowchart of the patients included in this study

Table 1: Baseline characteristics of the patients in the study based on Liver Frailty Index (LFI)

Parameter	Not frail (n=66)	Frail (n=54)	Overall (n=120)	P value
Age	42.53±7.92	44.85±12.32	43.57±10.16	0.215
Gender				
Female	11	13	24	0.313
Male	55	41	96	
Socio Economic Status				
Upper	1	1	2	0.179
Upper Middle	14	11	25	
Lower Middle	29	15	44	
Upper Lower	11	8	19	
Lower	11	19	30	
BMI Group				
Normal	47	22	69	0.001
Obese	2	1	3	
Overweight	7	4	11	
Underweight	10	27	37	
Comorbidity				
Diabetes	3	2	5	0.818
Hypertension	8	16	24	0.112
IHD	2	2	4	0.838
CKD	1	0	1	0.364
Pulmonary Tuberculosis	2	0	2	0.197
Tubercular	4	1	5	0.251
Abdominal Koch's	2	0	2	0.197
Etiology				
Alcohol	35	27	62	0.741
BCS	5	2	7	0.368
Hep B	11	12	23	0.442
Hep C	6	8	14	0.331
Nash Related	1	0	1	0.364
Not Known	8	7	15	0.890
Wilson Disease	2	2	4	0.838

Laboratory investigations

Table 2: Laboratory investigations based on frailty

Parameter	Not frail (n=66)	Frail (n=54)	P value
Hemoglobin	10.10±2.35	9.13±1.33	0.008
WBC	4658.93±2094.33	5743.70±2251.94	0.007
Platelet	2.42 [1.35, 63]	1.59 [1.12, 68]	0.401
T. Bilirubin	1.94±1.61	5.79±5.38	<0.0001
SGOT	86.57±56.03	97.14±44.01	0.261

SGPT	49.93±29.52	51.27±28.14	0.801
ALP	147.46±85.47	141.61±66.39	0.681
T. Protein	6.82±0.69	6.42±0.83	0.005
S. Albumin	3.21±0.83	2. 77±0.68	0.003
Sodium	137.00±4.31	135.70±4.86	0.125
Potassium	4.17±0.46	5.06±4.96	0.148
Urea	11.87±3.75	13.01±5.39	0.176
S. Creatinine	1.04±0.27	0.94±0.73	0.307
INR	1.55±0.30	1. 87±1.51	0.094

Table 3: Liver specific characteristics based on frailty

Parameter	Not frail (n=66)	Frail (n=54)	Overall (n=120)	P value
Hematemesis				
No	36	38	74	0.076
Yes	30	16	46	
Ascites				
No Ascites	42	8	50	<0.0001
Mild	18	5	23	
Moderate	6	23	29	
Severe	0	18	18	
CTP				
A	23	4	27	<0.0001
B	32	20	52	
C	11	30	41	
MELD	14.37±3.49	18.33±4.33	16.15±4.35	<0.0001
MELD Na	15.50±3.95	20.43±4.62	17.72±4.91	<0.0001

Association of frailty based on LFI with other scales

Table 4: Association of frailty based on LFI with other scales

Parameter	Not frail (n=66)	Frail (n=54)	P value
FFI			
Robust	48	0	<0.0001
Pre-Frail	15	11	
Frail	3	43	
CFI			
No	64	9	<0.0001
Yes	2	45	
SPPB			
No	63	1	<0.0001
Yes	3	53	
EFI			
Non-Frail	64	2	<0.0001
Vulnerable	1	15	
Mild Frailty	1	6	
Moderate	0	20	
Severe	0	11	
ECOG			
No	66	10	<0.0001
Yes	0	44	
KPS			
No	64	12	<0.0001
Yes	2	42	
IADL			
No	66	19	<0.0001
Yes	00	35	