

Is Liver Frailty and functional capacity associated with severity of liver disease in patients awaiting Liver Transplantation? - A prospective Observational Study

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ABSTRACT

Background: Liver is a major metabolic organ, interfering with the function of all organs and systems. So, the patients with severe liver disease may display wide manifestations of metabolic disorders, loss of muscle mass and function. Combination of these factors leads to decreased exercise tolerance and physical inactivity and it may be exaggerated with increasing severity of liver disease. The functional capacity could be severely affected due to multiple physiological derangements in these population. Hence, a liver transplant is the only cure for end stage liver disease. Currently only few literature are available that evaluated and described the status of frailty and functional capacity in these population. So we have tried to evaluate the same in Indian Population.

Methodology: After ethical committee approval and written inform consent, 85 cirrhotic patients who fulfilled the Inclusion and Exclusion criteria were included in the study. Disease specific history, Severity of Liver disease, Physical evaluation of frailty via Hand grip strength, Balance and time taken to do 5 chair stands, subjective functional capacity evaluation was done through Duke activity status Index (DASI).

Result: In 85 patients, the average Hand grip strength was 23.70 ± 10.60 kg in males and 15.02 ± 5.08 kg in females, average value of timed chair stands (TCS) was 18.18 ± 6.60 in males and 14.18 ± 8.65 in females, average balance score was 28.00 ± 4.99 in males and 29.33 ± 2.58 in females and the average value of MELDNa was 22.2 ± 6.9 .

Conclusion: When compared with normal Indian standard Liver cirrhotic patient, form of frailty and reduced functional capacity non predominant. That stressed emphasis on rehabilitation and nutritional counselling during waiting period for Transplantation.

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Access this Article online	Journal Information
Quick Response code  DOI: 10.16965/ijpr.2023.111	International Journal of Physiotherapy and Research ISSN (E) 2321-1822 ISSN (P) 2321-8975 https://www.ijmhr.org/ijpr.html DOI-Prefix: https://dx.doi.org/10.16965/ijpr 
	Article Information
	Received: 03 Feb 2023 Peer Review: 05 Feb 2023 Revised: 18 Mar 2023
	Accepted: 19 Mar 2023 Published (O): 11 Apr 2023 Published (P): 11 Apr 2023

INTRODUCTION

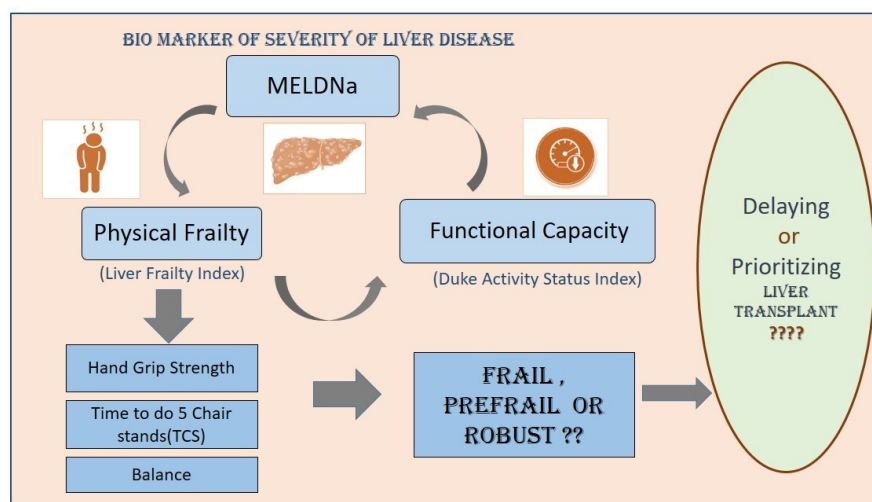
Liver plays an important role in metabolism, interfering with the function of almost all organs and systems. So, the patients with severe liver disease may display manifestations such as metabolic disorders, malnutrition, and loss of muscle mass and respiratory distress [1]. Currently, a liver transplant is the only cure for end stage liver disease. However the standard national criteria remains same, it may likely differ in each institute in terms of deciding who will be best benefitted from transplant, patients disease status, his/ her ability to sustain the stress of most complicated and stressful surgery. This factor stresses importance of evaluation of frailty and functional capacity before transplantation and anticipated planning for pre transplantation rehabilitation. Malnutrition, low skeletal muscle mass accelerated catabolism, hyper ammonia, physical inactivity, hyper metabolic state, protein energy deprivation are key component in physiological deterioration in liver cirrhotic subjects.

On the other hand; frailty has been associated with a combination of immunological and physiological impairments rather than a single biomarker. Frailty has also been defined in studies as presence of 3/5 criteria: weight loss, exhaustion weak grip strength, slow walking speed and physical activity [4-5].

Importantly, “physical frailty,” as investigated in patients with cirrhosis, is a critical determinant of adverse health outcomes in this population, including waitlist mortality, mortality

after liver transplantation, length of hospital stay and prolonged rehabilitation. To assess frailty in Pre transplant cirrhotic patients, there are various scales such as Fried frailty Index, Liver Frailty Index, Clinical Frailty Scale etc. In order to capture an accurate, quick, objective assessment of muscle strength and function (i.e. two key components of physical frailty) Lai et al. and colleagues devised the ‘Liver Frailty Index (LFI)’ in 2017 from a cohort of 536 patients with End Stage Liver Diseases and concluded that subjective clinical assessment alone can predict waitlist mortality, but addition of Liver Frailty Index significantly improved mortality risk prediction classifying 34% of the patients. (p=0.38) [5].

Evaluation of functional capacity on the other side is also necessary; as it’s a subjective matter and may or may not be affected due to cirrhosis with or without frailty. Duke activity status index is a self administered questionnaire used to assess the functional capacity of the patient. The activities in this scale represent major aspects of physical function – personal care, ambulation, household tasks, sexual function, and recreational activities. DASI has a good clinical correlation as it provides information about activities limited by the disease and its impact on patient’s life. It tells us in which aspect of functional activity patients life is hampered because of the disease [6,7].



METHODOLOGY

After ethical approval from IKDRC-ITS committee/15April/2019 and written informed consent, patients awaiting Liver Transplantation surgery who were referred to the physiotherapy department and those who fulfill the Inclusion – Exclusion Criteria were included in the study.

Inclusion Criteria: Patients awaiting Liver Transplantation who were between the age of 18-65 and who have got their recent lab reports done were included in the study.

Exclusion Criteria: Patients who had not got permission for any form of physical activity from liver transplant surgery unit, End stage organ disease other than liver, having acute exacerbation of chronic disease, Malignancy Including Hepatocellular carcinoma, Severe hepatic Encephalopathy, Any type of Myopathy, Neuropathy, Clinical evidence of or history of Cardiopulmonary, Neuromuscular, Rheumatological disease and severe osteoarthritis.

Patients details like – Age, Gender, Body weight, Abdominal Circumference and Clinical Data like Diagnosis of Disease and Recent Laboratory Reports for Model for End Stage Liver Disease Sodium (MELDNa) were taken into account.

Evaluation of Severity Of liver Disease:

A. Model for End Stage Liver Disease (MELDNa): MELD Score: $3.78 \times \ln(\text{Serum bilirubin mg/dl}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{Serum Creatinine mg/dl}) + 6.43$

MELDNa Score: MELD Score – SerumNa – $(0.0258 \text{ MELD Score} * (140 - \text{Serum}))$

B. Liver Frailty Index: At enrollment, all patients underwent a single baseline objective measurement of frailty [5].

Hand Grip strength: the average of 3 trials, measured in the subject's dominant hand – hand placed at 90 degrees elbow resting on the arm rest of the chair using Jammer hand held dynamometer [9].

Timed chair stands: measured as the number of seconds it takes to perform 5 chair stands with the subject's arms folded across the chest [10].

Balance testing: measured as the number of seconds that the subject can balance in 3 positions (feet placed side to side, semi-tandem, and tandem) for a maximum of 10 seconds each [10].

The LFI was calculated using the following equation

Formula: $= (-0.330 \times \text{gender} - \text{adjusted grip strength}) + (-2.529 \times \text{no. of chair stands per second}) + (0.040 \times \text{balance time}) + 6$.

Greater than or equal to 4.5 it's considered "FRAIL" or else it comes in the category of "PRE-FRAIL" [10].

Functional Capacity: Functional Capacity was evaluated with the help of Duke Activity Status Index (DASI) questionnaire. Original English version of DASI was translated into Hindi and Gujarati version after taking permission from Original Authors.

OUTCOME MEASURES

Liver Frailty Index Score (LFI): The Liver frailty Index score was used to measure frailty in the patient awaiting liver transplantation. Patient having scores less than 4.5 were considered prefrail and patients more than 4.5 were considered frail [5].

Duke Activity Status Index (DASI) Score – It was taken with the help of translated version of Duke Activity Status Index Score. DASI scale uses the patient's ability to perform a set of common activities of daily living to calculate functional capacity. The activities in the scale represent major aspects of physical function – personal care, ambulation, household tasks, sexual function, and recreational activities. These responses can also be used to assess physical limitations relevant to the patient's quality of life.

Statistical analysis:

Statistical analysis was performed using SPSS version 26. Data of all 85 participants with all these variables and outcome were analyzed for descriptive statistics and expressed as Mean \pm SD form. Data was analyzed for normality. As all the data behaved normal distribution, Pearson Correlation test was used for analysis between independent and dependent variable.

Table 1: Baseline characteristic of all patients.

Age (in Yrs.)	48.57± 9.27(Mean±SD)	
Gender(n=85)	Male (n=70)	Female (n=15)
Weight(In kg)	68.85 ± 16.70	65.95± 14.6
Mid-arm Girth (In cm)	24.01 ± 0.85 (Rt)	23.04 ± 2.58(Rt)
	24.01 ± 0.85(Lt)	23.04 ± 2.58 (Lt)
Mid-Thigh Girth(In cm)	41.02 ± 7.48(Rt)	39.1 ± 7.30(Rt)
	41.02 ± 7.48(Lt)	39.1 ± 7.30(Lt)
Abdominal Circumference (In cm)	100.2 ± 15.84	93.7 ± 18.08

Interpretation: The patients Gender, weight, Mid Arm girth, Mid-thigh girth, Abdominal Circumference was taken and is described in Mean ± SD form

Table 2: Patient’s classification according to type of Liver Disease.

Types of Liver Disease	Male	Female
Wilson’s disease	01(1.17%)	0
Non-alcoholic Steatohepatitis(NASH)	18(21.17%)	02(2.35%)
Cryptogenic liver disease	11(12.94%)	02(2.35%)
Alcoholic liver disease(ALD)	17 (20%)	0
Chronic liver disease(CLD)	23 (27.05%)	11(12.94%)

Interpretation: Here, 85 Patients were classified according to their condition. Out of them, only 1 male (1.17%) had Wilson’s disease. 18 Male (21.17%) and 2 Female (2.35%) had Non-alcoholic steatohepatitis related chronic liver disease (NASH-CLD).11 Male (12.94%) and 2 female (2.35%) had Cryptogenic Liver Disease.17 Male (20%) had Alcoholic Liver Disease.23 Male (27.05%) and 11 Female (12.94%) had Chronic Liver Disease

Table 3: Outcome measures of the Study.

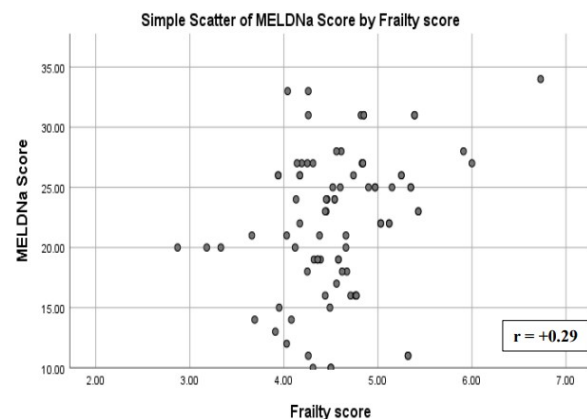
	Male	Female
Hand Grip Strength (In Kg)	23.70 ± 10.60	15.02 ± 5.08
Time to do 5 chair stands (In sec)	18.18 ± 6.60	14.18 ± 8.65
Balance (In sec)	28.00 ± 4.99	29.33 ± 2.58
Liver Frailty Index(LFI)	4.54 ± 0.60	4.79 ± 0.52
Meldna Score	22.15 ± 5.87	22.2 ± 6.19
DASII Score	23.78 ± 5.69	23.99 ± 16.85

Interpretation: The table 3 shows the outcome measures such as Hand Grip Strength (In Kg), Time to do 5 chair stands (In Sec), Balance (In sec), Liver Frailty Index (LFI), MELDNa Score and DASII Score which are shown in Mean ± SD Form.

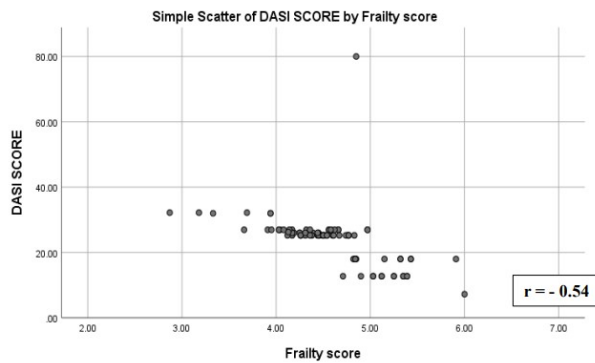
Table 4: Patients classification according to Liver Frailty Index.

	Frail	Prefrail	Robust
Male	37(43.53%)	32(37.64%)	02(2.35%)
Female	11(12.94%)	04 (4.71%)	-

Interpretation: The patients were classified into frail, prefrail and robust on the basis of cut-off criteria set by liver frailty index. Out of 85 patients, 37 male (43.53j) were found to be frail, 32 were prefrail (37.64%) and 02males (2.35%) were robust. 11 females (12.94%) were found to be frail, and 4 females (4.71%) were prefrail. The age was expressed in mean ± SD form which was 48.5±9.71 for males and 48.6 ± 7.29 for females.



Graph 1: Scatter plot Diagram showing correlation between Severity of Liver Disease and Liver Frailty (MELDNa Score vs. LFI), r = 0.29, p = 0.007



Graph 2: Scatter Plot Diagram showing correlation between functional capacity and Liver Frailty (DASI Score vs. LFI), $r = -0.54$, $p = 0.0004$

DISCUSSION

In our prospective observational Study, with 85 patients of Liver cirrhosis awaiting Liver Transplantation between were screened for severity of Liver Disease, Physical Frailty and Functional capacity. Out of 85 patients, 37 males were frail, 32 were prefrail and 02 were robust. Their average value of MELDNa was 22.15 ± 5.87 . Their average value of LFI was 4.54 ± 0.60 . In females, 11 were frail, 04 prefrail. Their average value of MELDNa was 22.2 ± 6.9 . In females, the average value of LFI was 4.79 ± 0.50 .

Similar to our study, Robyn Laube et al (2018) stated that Frail patients on the LT waitlist have significantly higher MELD scores compared to non-frail patients. They found out that increase proportionately with the severity of liver disease, with each point in the MELD-sodium score having a 0.04 coefficient with the Liver Frailty Index [11].

This somewhat justifies with the finding of our present study (MELD Na vs. LFI, $r = +0.29$, $p < 0.005$).

R P Mullerpatan et al (2014) documented normative data for healthy Indian adults which was 33.67 ± 7.2 kg in males and 19.51 ± 3.9 kg in females. In contrast to their study, present study participants had hand grip strength 23.70 ± 10.60 kg in males whereas 15.02 ± 5.08 kg in females which may be due to chronic liver disease related weakness.

In our population particularly, males their average value of timed chair stands was 18.18 ± 6.60 and average value of balance was 28.00 ± 4.99 .

In females, their average value of timed chair stands was 14.18 ± 8.65 and average value of balance was 29.33 ± 2.58 .

Seeing to the functional capacity a possible explanation for the reduction might be related to the loss of muscle mass in cirrhosis patients; however, the reduction in functional capacity may also be caused by the decrease in mitochondrial oxidative capacity and/or the number of mitochondria in the muscle tissue. Liver Dysfunction leads to protein and fat mal-absorption and hyper catabolic state [12]. So, Energy depletion when associated with physical inactivity lead to functional deterioration and hence Body Mass Index (BMI) is also found to be reduced in pre liver Transplant Recipients. Unfortunately, in our present study Body Mass Index was not taken and hence what effect it had on Liver Frailty Index was not seen.

Also, Assessment of functional capacity can be difficult in patients with end stage liver disease because of the high incidence of reduced mobility, physical deconditioning and obesity which may be also due to ascites and hence it would be difficult to account whether the increased abdominal circumference is due to ascites or because of obesity of the patient. As the liver transplantation is a major surgery lasting more than 12 hours, importance should be given to increase patient's functional capacity status preoperatively. Duke activity status index gives an idea of the patient's functional capacity and whether the patients would be at a higher risk for liver transplant surgery. It is easy to administer in pre liver transplant patients, takes few minutes and can be taken bed side. It's a 12 item questionnaire and is validated in patients with cardiac illness and incorporated in chronic kidney disease patients, chronic obstructive pulmonary disease patients in older literature.¹³

In present study, a correlation was done between duke activity index score of the patients (DASI) and the Liver Frailty Score (LFI) where a negative correlation was found between them as whenever the frailty increases, the patient becomes more frail resulting in more dependence, unable to carry out the activity of daily living.

Importantly, in our knowledge this is the first study evaluated and compared the MELDNa and Liver Frailty Index in Indian pre liver transplant recipients. In present study, most of the patient were frail and as such we were not able to find a strong correlation between severity of liver disease, frailty and functional capacity, larger cohort study should be conducted with long term follow up.

In summary, Liver Frailty Index (LFI) is a liver disease-specific, continuous variable (i.e. no ceiling or floor effect) that can then be categorised into frail, pre-frail and robust and assessed longitudinally. It has got dynamic ability to assess response to nutritional/exercise interventions. In doing so, indexes such as LFI could be used as a standard tool in all Liver Transplant units to facilitate clinical comparisons. It is, however, important to emphasise that there is no data support a single frailty cut-off at which a patient should not undergo Liver Transplant.

CONCLUSION

Liver Frailty index is useful tool for the assessment of functional deterioration and severity of liver disease in pre transplant recipients. Encourage assessment of LFI in cirrhotic patient as to shorten wait-list time. It establishes objective goal for pre transplant rehab. It sets the expectations of functional recovery after liver transplantation. This frailty index captures the multidimensional construct of frailty and improves the waitlist mortality over MELDNa alone.

Limitation: It was a single-Centre study. Also, Association of frailty and number of hospitalization admission before transplant and after transplant were not seen. The study did not measure whether frailty changed over time and with what will be the effect of lifestyle modification and exercise in this population.

ABBREVIATIONS

LFI: Liver Frailty Index

HGS: Hand Grip Strength

TCS: Time to do five chair stands

MELDNa: Model for end stage Liver Disease Sodium

DASI: Duke Activity Status Index

NASH: Nonalcoholic Steatohepatitis

ACKNOWLEDGEMENTS

We are thankful to all the patients who were enrolled in the study. I would like to thank all my coauthors and the entire Liver Transplant Surgery Unit for their continuous cooperation and support. I would like to dedicate this to my parents and especially to my father Late Sunil A. Vakani for his continuous support and encouragement throughout this journey.

Conflicts of interest: None

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How to cite this article: Nirali S. Vakani, Harda H. Shah, Pranjal Modi, Vaibhav Sutariya, Bharat Tiwari. Is Liver Frailty and functional capacity associated with severity of liver disease in patients awaiting Liver Transplantation? - A prospective Observational Study. *Int J Physiother Res* 2023;11(2):4476-4482. DOI: 10.16965/ijpr.2023.111