Untangling the Web of Malnutrition, Sarcopenia, and Frailty in Chronic Liver Disease

Malnutrition, sarcopenia, and frailty are overlapping yet distinct conditions that are very common among patients with liver cirrhosis, many of whom are prospective liver transplant recipients. Each condition has received well-merited attention, and abundant literature has accumulated regarding tools for assessing and grading each of these conditions, leading to some degree of confusion among practicing clinicians about which tools to use in which situations. A brief overview of these conditions will be helpful in appreciating two important papers appearing in this issue of the Journal.[1,2]

Malnutrition (synonymous with undernutrition in the present context) has been defined as "A nutrition-related disorder resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass, leading to diminished physical and mental function and impaired clinical outcome from disease."[3] This umbrella definition covers the whole spectrum of disorders of undernutrition commonly seen in advanced cirrhosis. The high prevalence of malnutrition (19.6% in men, 22.4% in women) in the Indian population reported in the National Family Health Survey-4 (NFHS-4, 2015–16) is alarming.[4] With this high background prevalence, it is not surprising that malnutrition is found in 30–100% of patients with liver cirrhosis, depending on the tools used to establish its presence.[5]

Complete nutritional assessment includes evaluation of muscle mass, use of global assessment tools, and a detailed dietary intake assessment. These are reviewed in detail elsewhere.[3,5] A variety of tools has been validated for various aspects of malnutrition. The Royal Free Hospital-nutritional prioritizing tool (RFH-NPT) score is a simple, bedside assessment tool that has been reported to correlate with clinical deterioration, the severity of disease (Child-Pugh score, model for end-stage liver disease [MELD] score), and clinical complications such as ascites, hepatorenal syndrome, and episodes of hepatic encephalopathy (HE). Improvement in RFH-NPT score was associated with improved survival.[6]

Sarcopenia, derived from the Greek *sarco* or flesh and *penia* or deficiency, literally means deficiency of flesh.[7] Earlier used to describe the age-related loss of skeletal muscle, today sarcopenia refers to skeletal muscle depletion leading to negative effects on physical performance and clinical outcomes across a broad range of disease states. Sarcopenia is subsumed within both malnutrition and frailty. It is a surrogate for severe malnutrition and is the dominant component of the frailty construct. It can be objectively measured in clinical practice and monitored serially. While the North American working group has restricted the definition of sarcopenia to depletion of skeletal muscle mass, other groups such as the European Working Group on Sarcopenia in Older People and Asian Working Group for Sarcopenia,[8,9] have incorporated muscle function (e.g., grip strength) and performance (e.g., gait speed) into the definition of sarcopenia. Various quantitative tools (CT scan, MRI scan, DEXA scan, bio-impedance analysis, ultrasonography) are available for the assessment of sarcopenia, and different cut-offs have been proposed for different populations.[10]

Due to differences in diet, body habitus, and physical activity, gender-specific sarcopenia cut-off values for skeletal muscle index at the 3rd lumbar vertebra (SMI-L3) have been found to be clearly lower in Indian subjects[11,12] than in the West,[8] making it abundantly clear that cut-off values established in the West are not suitable for use in India.

Frailty is a syndrome of loss of physiologic reserve in multiple body systems leading to increased vulnerability to health stressors that predispose to adverse health outcomes, notably disease, dependence, and death.[13] It is the end result of derangements of almost all important physiologic systems, including the liver, kidney, heart, etc., inflammatory, endocrine, cognitive, and musculoskeletal systems, as well as psychosocial factors.[13,14] The concept of frailty evolved in Geriatrics, centered around age-related physiological decline and focused on identifying services required in elderly patients, providing institutional care to them, planning interventions or predicting the risk of death in them. Thus, frailty in the elderly is a broad-based concept, incorporating cognitive, social, and emotional aspects along with physical frailty.[13,15]

The concept of frailty has been increasingly applied to areas of Medicine beyond Geriatrics and is finding resonance in the field of hepatology and liver transplantation. However, here the focus has been on developing tools for assessment of physical rather than cognitive frailty among cirrhotic patients. Although "cognitive frailty" is important in prognostication, it has been difficult to develop a

Abbreviations: ADL: Activities of Daily Living; BIA: Bioelectrical Impedance analysis; BMC: Bone Mineral Content; CFS: Clinical Frailty Score; DEXA: dual-energy X-ray absorptiometry; FFC: Fried Frailty Criteria; FM: Fat Mass; FFM: Fat-Free Mass; HE: hepatic encephalopathy; KPS: Karnofsky Performance Score; LFI: Liver Frailty Index; MAMC: mass and mid-arm muscle circumference; LM: Lean Mass; MELD: model for end-stage liver disease; SMI-L3: skeletal muscle index at the 3rd lumbar vertebra; SPPB: Short Physical Performance Battery; TSFT: triceps skinfold thickness; 6MWT: 6-minute walk test

https://doi.org/10.1016/j.jceh.2022.02.002

standardized tool for assessing it among cirrhotic patients and prospective liver transplant recipients due to the overlap with minimal or covert hepatic encephalopathy, which is likely to be the more important driver of cognitive dysfunction in this population rather than aging. On the other hand, physical frailty has repeatedly been shown to be a robust predictor of adverse health outcomes, including mortality (on the waitlist, after hospitalization, after liver transplantation), need for hospitalization, and length of hospital stay.[14,16] Thus, evaluation of frailty in Hepatology and liver transplantation has largely focussed on assessment and stratification of physical frailty. In fact, it has been proposed that frailty evaluation using a standardized frailty assessment tool should be part of the workup and optimization plan for every prospective liver transplant recipient.[5,14]

FRAILTY ASSESSMENT TOOLS AND CUT-OFF VALUES

The frailty assessment tools suggested by the North American Consensus include the Karnofsky Performance Score (KPS), Clinical Frailty Score (CFS), Activities of Daily Living (ADL) or Instrumental ADL (IADL), Liver Frailty Index (LFI), and the 6-minute walk test (6MWT) and has proposed cut-off values for each test.[14] INASL recommends the Liver Frailty Index as a tool for frailty assessment in cirrhotic patients.[5] LFI can be completed quickly (within 3 min) at the bedside, is objective and performance based, has a continuous scale without ceiling or floor effects and can be used in the outpatient setting. It provides repeatability after interventions, although the utility of the Δ-frailty metric has yet to be established. However, LFI has mainly been validated in the outpatient setting, and patient- or provider-assessed tools such as the Karnofsky Performance Status (KPS) and Activities of Daily Living (ADL) scale have been found useful in the inpatient setting. So, as proposed by Lai et al, it might be better to adopt a "frailty toolkit" (LFI, KPS, ADL, 6MWT) that will be valid in various settings where frailty assessment is needed.[14]

The INASL Consensus statement[5] has recommended that sarcopenia should be assessed using tests for muscle mass such as skeletal muscle index at the 3rd lumbar vertebra (L3-SMI), for muscle strength (dominant handgrip strength, HGS), and for performance (gait speed in the 4-meter walk test) using cut-off values established among Indian patients. INASL has proposed that the cut-off value for SMI-L3 on CT scan should be 42 cm^2/m^2 in men and 38 cm^2/m^2 in women; for dominant HGS, it should be 27 kg for men and 16 kg for women, while usual walking gait speed should be >0.8 m/s.

In summary, malnutrition forms the universal substratum in patients with liver cirrhosis. Sarcopenia is a marker of severe malnutrition and is the dominant factor determining physical frailty although it does not encompass all elements of frailty. Although frailty is a more broad-based concept, including cognitive frailty, as well as social and emotional aspects, frailty in CLD mainly refers to physical frailty. While malnutrition, sarcopenia, and frailty have all been shown to affect the need for hospitalization, mortality, and quality of life, frailty indices are relatively easy to use in the outpatient and inpatient settings, are repeatable, and provide a dynamic overview of the patient's overall condition.

Body composition analysis has been a tried and trusted method to establish the presence and severity of malnutrition. Dual-energy X-ray absorptiometry (DEXA) determines Fat Mass (FM), Lean Mass (LM), and Bone Mineral Content (BMC) while Bioelectrical Impedance analysis (BIA) measures only Fat Mass (FM) and Fat-Free Mass (FFM), the latter including bone, muscle, and total body water. In the present issue of the Journal, using DEXA as the reference test, Grover et al[1] have shown that BIA is as accurate in determining body composition of cirrhotic patients, at least in the population studied, which was largely ascites free. Authors have made a commendable effort to establish the utility of simple bedside anthropometric measures for assessing body composition in cirrhotic patients, specifically triceps skinfold thickness (TSFT) for subcutaneous fat mass and midarm muscle circumference (MAMC) for muscle mass. They have shown that TSFT and MAMC correlate well with FM and FFM measured by DEXA ($r = 0.69$, $r = 0.61$, respectively) and have also provided useful equations derived from data of Indian cirrhotic patients for measuring FM and FFM using TSFT and MAMC, respectively.

However, although anthropometry and BIA are easy to use and inexpensive, they are subject to interobserver and intraobserver variability and are better suited for single-time, cross-sectional assessment of nutritional status in large populations. These tests can at best be regarded as screening tools; abnormality should warrant a comprehensive assessment of the nutritional status of the patient. They lack the precision needed for serial monitoring of the nutritional status of an individual patient and to assess changes following dietary and exercise interventions.

In a prospective observational study, Singh and colleagues[2] have studied the impact of four **frailty assessment tools** [Liver Frailty Index (LFI), Short Physical Performance Battery (SPPB), Fried Frailty Criteria (FFC), Clinical Frailty Score (CFS)] on predicting mortality and hospitalizations in a cohort of 116 cirrhotic outpatients followed for 6 months. The primary outcome was the first of either all-cause unplanned hospitalization or all-cause mortality occurring within the study period of 6 months. Notable findings in this study were that frailty was present in 36–47% of Indian cirrhotic attending the outpatient clinic, that all four tools assessed were equally effective in assessing frailty, and that, as expected, frail patients had worse outcomes (92% hospitalization, 42% mortality at 6

months) than those who were not frail (6% hospitalization, 1.5% mortality). This study also highlighted the fact that including cognitive dysfunction did not improve predictions for hospitalization and mortality made on the basis of physical frailty alone.

This important study has reported a higher prevalence of frailty (36–47%) among CLD patients in India than in their western counterparts (21–25%),[17,18] which may be attributable to low socioeconomic status, poor nutrition, and late referrals. This is one of the few studies to perform a head-to-head comparison of various tools used for assessing physical frailty. The authors' finding that these tools were comparable for predicting hospitalization and mortality is reassuring and allows flexibility in clinical application.

In addition to study limitations pointed out by the authors, it seems that adding sarcopenia assessment using Indian cut-off values, as suggested in the INASL Consensus,[5] would have added greater value to this study. Validated cut-offs for muscle mass such as SMI-L3 by CT scan and for muscle function tests such as handgrip strength, gait speed, and chair stands are now available from Indian populations,[11,12,19] which would have corrected for the use of Western cut-off values for these tests used in the present study. Stratifying frailty into mild, moderate, and severe grades, as proposed by Lai et al,[14] could have further added value to this study by helping to establish whether just the frequency or also the severity of frailty is greater among Indian patients with CLD. In fact, it would be relevant to determine futility cut-offs for cirrhotics with severe frailty to identify those unable to perform the basic exercises that may improve frailty. As noted by the authors, no effective pharmacologic intervention is available for frailty, and diet and exercise remain the mainstay of therapy.

Although no interventions were offered in the present study, the need to undertake studies documenting the impact of interventions on frailty metrics and the impact of improved frailty on outcome after LT is self-evident. The development and validation of frailty assessment tools for Indian patients allows clinicians to identify frailty and to offer effective interventions earlier in the course of cirrhosis. With the concept of "prehabilitation" finding increasing acceptance prior to major abdominal surgeries, including LT,[20–22] the time is now ripe for incorporating these tools into a formal baseline assessment and longitudinal follow-up plan for diet and exercise interventions among cirrhotic patients. Initiating multicentric studies that use a multidisciplinary prehabilitation approach with appropriate monitoring will allow clinicians to offer effective interventions that have a meaningful impact on the outcome in prospective LT recipients, as well as those who are not candidates for LT.

CONFLICTS OF INTEREST

The authors have none to declare.

FUNDING

None.

REFERENCES

1. Grover I, Singh N, Gunjan D, Pandey RM, Sati HC, Saraya AN. Comparison of anthropometry, bioelectric impedance and dual energy X-ray absorptiometry for body composition in Cirrhosis. *J Clin Exp Hepatol*. 2021 https://doi.org/10.1016/j.jceh.2021.05.012.
2. Singh S, Taneja S, Tandon P, et al. A comparison of different frailty scores and impact of frailty on outcome in patients with cirrhosis. *J Clin Exp Hepatol*. 2021 https://doi.org/10.1016/j.jceh.2021.07.003.
3. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70:172–193.
4. Dutta M, Selvamani Y, Singh P, et al. The double burden of malnutrition among adults in India: evidence from the National Family Health Survey-4 (2015-16). *Epidemiol Health*. 2019;41e2019050.
5. Puri P, Dhiman RK, Taneja S, et al. Nutrition in chronic liver disease: consensus statement of the Indian National Association for Study of the Liver. *J Clin Exp Hepatol*. 2021;11:97–143.
6. Borhofen SM, Gerner C, Lehmann J, et al. The Royal Free Hospital-nutritional prioritizing tool is an independent predictor of deterioration of liver function and survival in cirrhosis. *Dig Dis Sci*. 2016;61:1735–1743.
7. Carey EJ, Lai JC, Sonneday C, et al. *Hepatology*. 2019 November;70:1816–1829. https://doi.org/10.1002/hep.30828.
8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. *Age Ageing*. 2010;39:412–423 [PubMed: 20392703].
9. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian working group for sarcopenia. *J Am Med Dir Assoc*. 2014;15:95–101 [PubMed: 24461239].
10. Anand A, Saraya A. Assessment of sarcopenia in chronic liver disease: Indian perspective. *Clin Liv Dis*. 2021;18:164–167.
11. Benjamin J, Shasthry V, Kalal CR, et al. Characterization of body composition and definition of sarcopenia in patients with alcoholic cirrhosis: a computed tomography based study. *Liver Int*. 2017;37:1668–1674.
12. Sidhu S, Saggar K, Goyal O, et al. Normative values of sarcopenia in the Indian population. Indian Society of Gastroenterology. *Indian J Gastroenterol*. 2018;37:1–137.
13. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Ser A, Biol Sci Med Sci*. 2001;56:M146–M156.
14. Lai JC, Sonnenday C, Tapper EA, 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 July;19:1896–1906. https://doi.org/10.1111/ajt.15392.
15. Rockwood K, Xong S, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J*. 2005;173:49–95. https://doi.org/10.1503/cmaj.050051.
16. Tandon P, Tangri N, Thomas L, 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 Dec;111:1759–1767.
17. Skladany L, Molcan P, Vnencakova J, Vrbova P, Kukla M, Laffers L, Koller T. Frailty in Nonalcoholic Fatty Liver Cirrhosis: A Comparison with Alcoholic Cirrhosis, Risk Patterns, and Impact on Prognosis. *Can J Gastroenterol Hepatol*. 2021;2021:10. https://doi.org/10.1155/2021/5576531. Article ID 5576531.
18. Lai JC, Rahimi RS, Verna EC, et al. Frailty associated with waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study. *Gastroenterology*. 2019;156:1675–1682.

19. Sidhu SS, Saggar K, Goyal O, et al. Muscle strength and physical performance, rather than muscle mass, correlate with mortality in end-stage liver disease. *Eur J Gastroenterol Hepatol*. 2021 Apr 1;33:555–564. https://doi.org/10.1097/MEG.0000000000001761.
20. Volk ML, Sonnenday C. Patient-centered liver transplantation. *Clin Liver Dis*. 2016;8:24–27.
21. Duarte-Rojo A, Ruiz-Margáin A, Montano-Loza AJ, Macías-Rodríguez RU, Ferrando A, Kim WR. Exercise and physical activity for patients with end-stage liver disease: improving functional status and sarcopenia while on the transplant waiting list. *Liver Transpl*. 2017;24:122–139.
22. Tandon P, Ismond KP, Riess K, et al. Exercise in cirrhosis: translating evidence and experience to practice. *J Hepatol*. 2018;69:1164–1177 [PubMed: 29964066].

Vivek A. Saraswat
Karan Kumar
Department of Hepatology, Pancreato-biliary Sciences and Liver Transplantation, Mahatma Gandhi Medical College and Hospital, Jaipur Rajasthan 302022, India

Address for correspondence. Professor Vivek A. Saraswat, Department of Hepatology, Pancreato-biliary Sciences, and Liver Transplantation, Mahatma Gandhi Medical College and Hospital, RIICO Industrial Area, Sitapura, Jaipur 302022, India.
E-mail: profviveksaraswat@gmail.com (V. A. Saraswat)