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ORIGINAL ARTICLE

Clinical utility of the liver frailty index for predicting sarcopenia in chronic liver disease patients with hepatocellular carcinoma.

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ABSTRACT… Objective: To determine the accuracy of liver frailty Index (LFI) to predict sarcopenia in patients of chronic liver disease (CLD) with hepatocellular Carcinoma (HCC). **Study Design:** Cross-sectional study. **Setting:** Outpatient Department of the Gastroenterology, Liaquat National Hospital, Karachi, Pakistan. **Period:** August 2022 to February 2023. **Methods:** A total of 110 patients aged 45-70 years, having CLD with HCC were analyzed. Frailty was classified on the basis of LFI as robust (< 3.2), prefrail (3.2-4.4), and frail (≥ 4.5). Muscle atrophy was evaluated by skeletal mass muscle index (SMI) evaluated through CT scan at L3 region. **Results:** In a total of 110 patients, 62 (56.4%) were male. The mean age was 57.93±6.86 years. The mean LFI was 3.93±0.76. Forty-five (40.9%) patients were classified as frail. The distribution of frailty was not significantly with respect to gender (p=0.649), or CLD type (p=0.788). Child Pugh classification (p<0.001), and HCC staging (p<0.001) were found to have significant association with frailty. Sarcopenia was documented in 74 (67.3%) patients with HCC. Gender (p=0.183), BMI (p=0.533), and CLD types (p=0.448) were not found to have any significant association with sarcopenia. Child-Pugh classification (p<0.001), and HCC staging (p<0.001) were having significant association with sarcopenia. Frailty was found to depict significant linkage with sarcopenia (p<0.001). **Conclusion:** Frailty, as assessed by LFI, shows a strong association with sarcopenia, independent of gender and CLD type. Child-Pugh classification and HCC stage were identified as important predictors of both frailty and sarcopenia.

Key words: Chronic Liver Disease, Frailty, Hepatitis C, Hepatocellular Carcinoma, Sarcopenia.

INTRODUCTION

Liver cirrhosis causes significant morbidity and mortality all around the globe. Annually, chronic liver diseases contribute to approximately 2 million deaths worldwide.[1,2] The combination of cirrhosis and liver malignancies influence around 3.5% of global fatalities, making it the 3rd leading cause of morality in 45-65 years age group.[3] There has been a significant increase in research that has identified sarcopenia (SP) and frailty as common complications in cirrhosis that can predict morbidity and mortality. These complications have the potential to be modified if detected early and treated appropriately.[4] Therefore, it is crucial for clinicians to have a comprehensive understanding of SP and frailty, including their measurement methods, impact on prognosis and decompensation, underlying pathophysiology, and the recommended treatment approaches.

The incidence of SP in "liver cirrhosis (LC)" has been documented to range from 30-70%, a significantly higher rate compared to the approximately 20% observed in inflammatory bowel diseases, which are known to be typical causes of secondary SP.[5-7] Protein-energy malnutrition has been identified as the underlying mechanism of SP in LC patients. Loss of appetite is commonly observed in individuals with acute or chronic liver problems, and the presence of ascites can further contribute to early satiety. Cirrhosis can often lead to maldigestion due to reduced bile salt solubilisation.[8]

Frailty refers to an elevated susceptibility to stressors caused by a decline in reserve,

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resistance, and inadequate homeostasis, which significantly impacts both health status and the functioning of multiple organs. In the context of "chronic liver disease (CLD)", frailty is being extensively examined and regarded as indicative of compromised overall physical performance.[9] The "liver frailty index (LFI)" is used to assess the frailty status in CLD encompassing the evaluation of grip strength, chair stands, and balance setting.[10,11]

The SP and frailty are conditions characterized by the depletion of body tissues. Diminished strength and functionality are prevalent characteristics of both SP and frailty.[12] Frailty can be identified through various symptoms, such as decreased physical activity and persistent fatigue.[13] A study from Japan revealed the prevalence of SP in CLD as 24.0%.[14] There is no local literature exploring the association SP and LFI in CLD patients. This study aimed to find out the accuracy of LFI to predict SP in CLD patients with hepatocellular carcinoma (HCC).

METHODS

This cross-sectional study was done at the outpatient department of Gastroenterology, "Liaquat National Hospital & Medical College, Karachi", Pakistan, from August 2022 to February 2023. The study commenced after obtaining approval from the ethical committee of the institution (0766-2022 LNH-ERC, dated: 28th March, 2022). A sample size of 110 was calculated considering the prevalence of SP in CLD as 24.0%[14], with 95% confidence level and 8% margin of error. The inclusion criteria were patients of either gender, aged 45-70 years, who had a confirmed diagnosis of CLD with HCC. The exclusion criteria were patients with hepatic encephalopathy grade ≥ 2. Those with history of cardiovascular accident, or having musculoskeletal diseases, or those who were unable to undergo LFI evaluation were also excluded. Written and informed consents were obtained from all patients. Non-probability, consecutive sampling technique was adopted.

Frailty classification was based on established LFI cut-offs: robust (<3.2), prefrail (3.2-4.4), and frail (≥4.5).[11] The LFI formula is: "(-0.330 × sex-adjusted grip strength) + (-2.529 × chair stands per second) + (-0.040 × balance time) + 6".[15] Grip strength was measured in kilograms with a handheld dynamometer, averaging three trials. Chair stands were timed for the subject to complete five stands with arms crossed, while balance was assessed by timing the subject's ability to maintain three positions (side-to-side, semitandem, tandem) for a maximum of 10 seconds each. Muscle atrophy was determined by "skeletal muscle index (SMI)", calculated through CT scan at the L3 region, using cut-off values of males<42 cm^2/m^2, and females<38 cm^2/m^2.[16] BMI (kg/m^2) was classified as "underweight (<18.5)", "normal (18.5-24.9)", "overweight (25.0-29.9)", or "obese (≥30.0)". The statistical analysis was performed using "IBM SPSS Statistics, version 26.0". The quantitative variables were expressed as mean and standard deviation. The qualitative variables were presented as frequency and percentages. Chi-square test was used to compare data, considering $p<0.05$ as significance.

RESULTS

In a total of 110 patients, 62 (56.4%) were male. The mean age, BMI, and duration of disease, were 57.93±6.86 years, 24.72±2.68 kg/m^2, and 56.34±22.05 months, respectively. The mean MELD-Na, and frailty scores were 18.55±7.23, and 3.93±0.76, respectively. The mean LFI was 3.93±0.76. Forty-five (40.9%) patients were classified as frail (Table-I).

The distribution of frailty was not significantly with respect to gender ($p=0.649$), or CLD type ($p=0.788$). Child Pugh classification ($p<0.001$), and HCC stages ($p<0.001$) were found to have significant association with frailty, and the detailed description is shown in Table-II.

The SP was documented in 74 (67.3%) patients with HCC. Gender ($p=0.183$), BMI ($p=0.533$), and CLD types ($p=0.448$) were not having significant association with SP. Child-Pugh classification ($p<0.001$), and HCC staging ($p<0.001$) had significant association with SP. Frailty was found to depict significant association with SP ($p<0.001$), as shown in Table-III.

Characteristics		Frequency (%)
Gender	Male	62 (56.4%)
	Female	48 (43.6%)
BMI	Underweight	2 (1.8%)
	Normal	54 (49.1%)
	Overweight	52 (47.3%)
	Obese	2 (1.8%)
Chronic liver disease type	Alcoholic	10 (9.1%)
	Seronegative	31 (28.2%)
	HBV	29 (26.4%)
	HCV	33 (30.0%)
	Non-alcoholic fatty liver disease	3 (2.7%)
	Autoimmune	2 (1.8%)
	HBV and HCV	1 (0.9%)
	Others	1 (0.9%)
Child-Pugh class (Liver severity index)	A	14 (15.5%)
	B	59 (53.6%)
	C	34 (30.9%)
Hepatocellular carcinoma stage (Liver severity index)	Early	39 (35.5%)
	Intermediate	38 (34.5%)
	Advanced	23 (20.9%)
	Terminal	10 (9.1%)
Frailty	Robust	22 (20.0%)
	Pre-frail	43 (39.1%)
	Frail	45 (40.9%)
Sarcopenia	Yes	74 (67.3%)
	No	36 (32.7%)

Table-I. Demographic and clinical characteristics (n=110)

Characteristics		Frailty			P-Value
		Robust (n=22)	Pre-frail (n=43)	Frail (n=45)	
Gender	Male	13 (59.1%)	26 (23.7%)	23 (51.5%)	0.649
	Female	9 (40.9%)	17 (15.5%)	22 (48.5%)	
Chronic liver disease type	Alcoholic	-	6 (14.0%)	4 (8.9%)	0.788
	Seronegative	6 (27.3%)	12 (27.9%)	13 (28.9%)	
	HBV	8 (36.4%)	9 (20.9%)	12 (26.7%)	
	HCV	6 (27.3%)	13 (30.2%)	14 (31.1%)	
	Non-alcoholic fatty liver disease	1 (4.5%)	1 (2.3%)	1 (2.2%)	
	Autoimmune	1 (4.5%)	1 (2.3%)	-	
	HBV and HCV	-	1 (2.3%)	-	
	Others	-	-	1 (2.2%)	
Child-Pugh classification	A	11 (50.0%)	5 (11.6%)	1 (2.2%)	<0.001
	B	10 (45.5%)	31 (72.1%)	18 (40.0%)	
	C	1 (4.5%)	7 (16.3%)	26 (57.8%)	
Hepatocellular carcinoma stage	Early	21 (95.4%)	17 (39.5%)	1 (2.2%)	<0.001
	Intermediate	1 (4.5%)	20 (46.5%)	17 (37.8%)	
	Advance	-	4 (9.3%)	19 (42.2%)	
	Terminal	-	2 (4.7%)	8 (17.8%)	

Table-II. Association of frailty with demographic and clinical characteristics (n=110)

Characteristics		Sarcopenia		P-Value
		Yes (n=74)	No (n=36)	
Gender	Male	39 (52.7%)	23 (63.9%)	0.183
	Female	35 (47.3%)	13 (36.1%)	
BMI	Underweight	2 (2.7%)	-	0.553
	Normal	35 (47.3%)	19 (52.8%)	
	Overweight	35 (47.3%)	17 (47.2%)	
	Obese	2 (2.7%)	-	
Chronic liver disease type	Alcoholic	7 (9.6%)	3 (8.3%)	0.488
	Seronegative	21 (28.4%)	10 (27.8%)	
	HBV	15 (20.3%)	14 (38.9%)	
	HCV	26 (35.1%)	7 (19.4%)	
	Non-alcoholic fatty liver disease	2 (2.7%)	1 (2.8%)	
	Autoimmune	1 (1.4%)	1 (2.8%)	
	HBV and HCV	1 (1.4%)	-	
	Others	1 (1.4%)	-	
Child-Pugh classification	A	4 (10.8%)	13 (36.1%)	<0.001
	B	40 (54.1%)	19 (52.8%)	
	C	3 (4.1%)	4 (11.1%)	
Hepatocellular carcinoma stage	Early	12 (16.2%)	27 (75.0%)	<0.001
	Intermediate	32 (43.2%)	6 (16.7%)	
	Advance	23 (31.1%)	-	
	Terminal	7 (9.6%)	3 (8.3%)	
Frailty	Robust	-	22 (61.1%)	<0.001
	Pre-frail	32 (43.2%)	11 (30.6%)	
	Frail	42 (56.8%)	3 (8.3%)	

Table-III. Association of sarcopenia with demographic and clinical characteristics (N=110)

DISCUSSION

This study revealed the mean age of HCC patients as 57.93±6.86 years. In a study by Munaf et al, the mean age of patients with HCC was described as 52.35±11.9 years.[17] Similar findings (56.24±13.65 years) were reported by Abbasi et al in another local study.[18] The male-to-female ratio in this study was 1.3:1, with males being predominantly involved, similar to the observed male proportion by others.[19] In this study, HCV was the leading cause behind HCC with contribution to 30% cases, while HBV was the cause in 26.4% patients. The risk factors for HCC differ significantly based on the geographical location. It is evident that the incidence rates of HCC are influenced by various factors, including race/ethnicity, gender, age, and geographic and demographic regions.[20,21] The spread of the HCV is linked to factors such as rural population, low literacy rates, unchecked blood transfusions, and misuse of injectable medications.[22]

Frailty is becoming more widely acknowledged as a significant prognostic indicator for individuals with advanced liver disease.[23] The LFI is a verified and objective assessment performed at the bedside, and was created at "University of California, San Francisco".[24] The LFI has demonstrated its ability to forecast the survival rates of patients on the LT waiting list, or with decompensated disease, and risk of re-hospitalization.[24,25] LFI was found to be correlated with SMI in this study. Muscle atrophy in CLD patients with HCC was independently associated with frailty/pre-frailty based on LFI. LFI could serve as a valuable screening tool for muscle atrophy in CLD patients with HCC, even when grip strength appears normal. According to the criteria used to assess sarcopenia, 67.3% of the patients in this study were having SP. The study conducted by Nagamatsu et al[26] revealed that the prevalence of SP was reported as 29.9% in patients with HCC. The research conducted by Tandon et al[4] found that 57.0% patients with cirrhosis who had

sarcopenia were men, indicating a significant gender disparity. Liu J et al[27] observed SP in a higher proportion in men (71.0%) compared to women (49.0%) with cirrhosis.

In this study, the mean BMI among HCC patients was 24.96±2.14 kg/m^2. This relatively high BMI suggests that these patients may have a higher proportion of muscle mass compared to fat. This finding is significant because SP is a common complication in HCC and associated with poor outcomes. Therefore, the presence of a higher BMI in these patients could potentially indicate a protective effect of muscle mass against SP and its associated negative consequence.[28,29] The study was performed in HCC patients at a single study center, so population bias may exist, and these were some inherent limitations of this study.

CONCLUSION

Frailty, as assessed by LFI, shows a strong association with sarcopenia, independent of gender and CLD type. Child-Pugh classification and HCC stage were identified as important predictors of both frailty and sarcopenia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Lubna Kamani:** Conception and designed, Critical revisions, Proof reading, Approved the final draft for publication.
2	**Attique Rahman:** Data collection, Drafting, Responsible for data's integrity, Approved for publication.
3	**Muhammad Ali:** Daata collection, Data analysis, Critical revisions, Approved for publication.
4	**Mehreen Akmal:** Data collection, Data synthesis, Literature review, Proof reading, Approved for publication.