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"Assessing the Relationship between Sarcopenia and Liver Disease Severity in Child-Pugh A and B Patients"

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KEYWORDS

Nutritional Status, Sarcopenia, Child-Pugh Classification and Liver Cirrhosis.

ABSTRACT:

Introduction: The incidence of liver diseases is increasing, and it may be a severe subsequent lifestyle disease. About 50-90% of patients with cirrhosis can have malnutrition. Managing this malnutrition is vital to facilitate clinical outcomes among cirrhotic patients. Sarcopenia is also associated with poor outcomes among patients with cirrhosis.

Aims: To assess the nutritional status in patients with Child-Pugh A and B cirrhosis of the liver. To assess the proportion of sarcopenia in patients with Child-Pugh A and B cirrhosis of the liver. To study the correlation of sarcopenia with the severity of liver cirrhosis.

Materials & Methods: The present study was a Cross-sectional study. This Study was conducted from October 2019 to December 2020 at Outpatients and inpatients of the Department of Medical Gastroenterology at King George Hospital, Andhra Medical College, Visakhapatnam. Total 100 patients were included in this study.

Result: Anthropometric indicators Triceps skin fold, Mid arm muscle circumference, and Body mass index were used for nutrition assessment. Mean±SD of TSF was 14.1±2.4 with the range of 10-22mm. MAMC ranged from 11.1-27.3 mm with a mean±SD of 19.9±3. BMI ranged from 15.4-31.3 kg/m2 with a mean±SD of 21.4±3.1. A total of 46 patients had below normal TSFT. MAMC was below the usual cut-off in 45 patients. BMI was low in 33 patients.

Conclusion: Sarcopenia is prevalent in the studied cirrhotic patients causing limitation of activities and increases the risk of fall. It was more commonly seen in middle-aged men. The commonest etiology of cirrhosis in sarcopenia was alcohol.

INTRODUCTION

The incidence of liver diseases is increasing, and it may be a severe subsequent lifestyle disease [1]. About 50-90% of patients with cirrhosis can have malnutrition. Managing this malnutrition is vital to facilitate clinical outcomes among cirrhotic patients. Sarcopenia is also associated with poor outcomes among patients with

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cirrhosis [2]. The pathogenesis of sarcopenia is multifactorial. Nutritional imbalances need to be treated with physical and pharmacological interventions to reverse sarcopenia and to improve their outcomes. Despite the great relevance of malnutrition, its diagnosis can be troublesome in patients with cirrhosis and may go unrecognized. Sarcopenia in CLD is the most common and frequently unseen complication, has a negative impact on quality of life, survival, and response to a stressor, such as infections and surgeries in patients with liver cirrhosis [3]. Sarcopenia assessment and intervention for improving performance status should be essential in managing patients with liver cirrhosis. The clinical significance of sarcopenia and its correlation with the severity of liver disease is little explored in the Indian context. It is easier to acquire details among Child A and Child B cirrhotics and knowledge of their nutritional status and severity of liver disease can help guide early interventions and patient care.

To assess the nutritional status in patients with Child-Pugh A and B cirrhosis of the liver. To assess the proportion of sarcopenia in patients with Child-Pugh A and B cirrhosis of the liver. To study the correlation of sarcopenia with the severity of liver cirrhosis.

MATERIALS AND METHODS

Study design: Cross-sectional study

Study duration: October 2019 to December 2020

Study population: 100

Study Site: Outpatients and inpatients of the Department of Medical Gastroenterology at King George Hospital, Andhra Medical College, Visakhapatnam

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

- All adult patients aged 18 - 65 years evaluated for cirrhosis of the liver and found to have Child-Pugh A and B severity

Exclusion criteria

- Liver Cirrhosis patients with Child Pugh-C
- Active comorbid disease, e.g., pulmonary, cardiovascular, renal disease (especially hepatorenal syndrome)
- Malignancy
- HIV
- Hepatic encephalopathy
- Pregnancy
- Acute hepatitis
- Refusal of consent

Statistical Analysis:

For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests, which compare the means of independent or unpaired samples, were used to assess differences between groups. Paired t-tests, which account for the correlation between paired observations, offer greater power than unpaired tests. Chi-square tests (χ^2 tests) were employed to evaluate hypotheses where the sampling distribution of the test statistic follows a chi-squared distribution under the null hypothesis; Pearson's chi-squared test is often referred to simply as the chi-squared test. For comparisons of unpaired proportions, either the chi-square test or Fisher’s exact test was used, depending on the context. To perform t-tests, the relevant formulae for test statistics, which either exactly follow or closely approximate a t-distribution under the null hypothesis, were applied, with specific degrees of freedom indicated for each test. P-values were determined from Student's t-distribution tables. A p-value ≤ 0.05 was considered statistically significant, leading to the rejection of the null hypothesis in favour of the alternative hypothesis.

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RESULT

Table 1: Severity grading of cirrhosis

Parameter		**Number of patients (n=100)**	**Male n(%)**	**Female n (%)**
CTP class	CTP class A	41	33(80)	8(20)
	CTP class B	59	36(61)	23(39)
MELD score	<15	72	46(64)	26(36)
	>15	28	23(82)	5(18)

Table 2: Anthropometry parameters of patients

Variables	**Minimum**	**Maximum**	**Mean±SD**	**Below normal cut-off (%)**
Triceps skinfold (mm)	10	22	14.1±2.4	46
MAMC (mm)	11.1	27.3	19.9±3	45
BMI ($kg/m^{2)}$	15.4	31.3	21.4±3.1	33

Table 3: Sarcopenia Assessment parameters

Variables	**Mean±SD**	**Min**	**Max**	**% abnormal of total patients**
Handgrip strength (kg)	25.8±6.3	11.6	36	31
Gait Speed (m/sec)	0.87±0.19	0.6	1.3	26
CT PMTH (mm/m)	17±2.2	13.2	22.1	44

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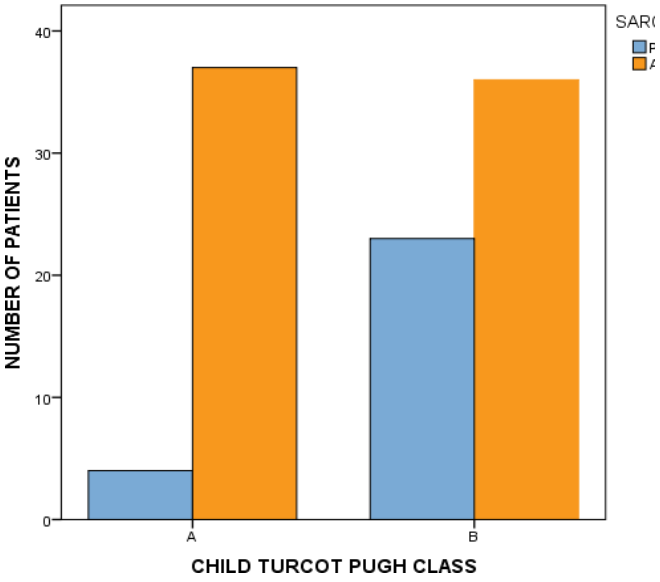
Figure 1: Bar diagram for association of Child-Turcotte-Pugh class with sarcopenia



The Child-Turcotte-Pugh (CTP) score was child class A in 41% of patients, while Child class B was in 59% of patients. MELD score<15 was seen in 72% of patients. The majority of the males, 23(82%), had MELD score > 15.

Anthropometric indicators Triceps skin fold, Mid arm muscle circumference, and Body mass index were used for nutrition assessment. Mean±SD of TSF was 14.1±2.4 with the range of 10-22mm. MAMC ranged from 11.1-27.3 mm with a mean±SD of 19.9±3. BMI ranged from 15.4-31.3 kg/m^2 with a mean±SD of 21.4±3.1. A total of 46 patients had below normal TSFT. MAMC was below the usual cut-off in 45 patients. BMI was low in 33 patients.

The handgrip strength was abnormal in 31/100 (31%) patients. Gait speed was reduced in 26/100 (26%) patients, and CT PMTH was abnormal in 44 patients. The mean of handgrip strength was 25.8±6.3 kg, the mean of Gait speed was 0.87±0.19 m/sec, and the mean of CT PMTH was 17±2.2 mm/m.

In CTP class A, 4(14.8%) patients had sarcopenia. In CTP class B, sarcopenia was seen in 23(85.2%) patients. There was a significant association seen between Child- Turcotte-Pugh class and sarcopenia with **p=0.001.**

DISCUSSION

Sarcopenia is defined as reduced skeletal muscle strength, mass, and function that often occurs in cirrhotic patients [3]. It is associated with increased mortality, a higher rate of complications and poorer outcomes in patients with hepatocellular carcinoma.

Nutritional status in patients with Child-Pugh A and B cirrhosis was assessed in this study. We also studied the proportion of sarcopenia in patients with Child-Pugh A and B cirrhosis of the liver and the correlation of sarcopenia with the severity of liver cirrhosis.

The outcomes of 100 patients were studied. The Mean age of patients studied was 47.9±11.5 years with a range of 18-65 years. The majority of the 34(34%) patients were in the age group of 41-50 years. This means that the commonest group of individuals affected are those who were in their prime working life. Male predominance was seen in this study, with 69(69%) of patients being males, with a male: female ratio of 2.2:1. The mean ± SD of BMI was 21.4±3.1 kg/m2. The results are almost similar to those seen across the world.

The etiology of cirrhosis was alcohol-related cirrhosis in 51% of patients; NASH in 10% of patients; Hepatitis B virus-related cirrhosis in 14% of patients; hepatitis C virus- related cirrhosis in 10%; autoimmune hepatitis in 3%. In comparison, it was unknown in 12% of patients. There was no significant association between the various etiologies for chronic liver disease and sarcopenia (p=0.655).

CTP and MELD scores have been widely used as prognostic indicators of liver disease in all the studies. The Child-Turcotte-Pugh (CTP) score was child class A in 41% of patients, while Child class B was in 59% of patients. MELD score<15 was seen in 72% of patients. The majority of the males, 23(82%), had MELD score > 15.

We used anthropometric indicators, namely triceps skinfold thickness, mid-arm muscle circumference, and body mass index, for nutritional assessment. TSFT ranged from 10-22 mm with a mean±SD of 14.1±2.4. MAMC ranged from 11.1-27.3 mm with a mean±SD of 19.9±3. BMI ranged from 15.4-31.3 kg/m2 with a mean±SD of 21.4±3.1. A total of 46 patients had below normal TSFT (TST <12.5mm for males and <18mm for females were considered abnormal). MAMC was below

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the normal cut-off in 45 patients [MAMC values <21.1cm for males and <19.2cm for females were considered abnormal, and patients were diagnosed with malnutrition]. BMI was low in 33 % patients [BMI values < 18.5 kg/m2 were considered abnormal].

The Association of TSFT with gender, alcohol intake, and MELD score were significant (P<0.05). In contrast, the association of TSFT with Ascites and CTP score was not significant. The association of MAMC was significant only with ascites (P<0.05), whereas it was not significant with gender, alcohol intake, CTP, and MELD score. In contrast, the association of BMI was not significant with any of the above parameters.

As reported in the literature, patients with sarcopenia can have inadequate nutrients intake and result in muscle weakness, limiting physical exercise, and perpetuating the reduction of muscle mass [3]. In a recent north Indian study in 2018, the authors studied malnutrition in patients with liver disease. Patients with cirrhosis (n = 352), chronic hepatitis (n = 189) and healthy controls (n = 159) were enrolled in study. Malnutrition was diagnosed based on a subjective global assessment (SGA) score. According to SGA, 24% of patients with chronic hepatitis and 56% of patients with cirrhosis had malnutrition (P = 0.001). The prevalence of malnutrition according to MAMC was 12% and according to TST was 31% in chronic hepatitis patients [4].

Nunes G et al. in 2017 [5] studied nutritional assessment of CLD patients using anthropometry. A total of 130 CLD patients (80 men) aged 22-89 years (mean 60 years) were included. Most suffered from alcoholic cirrhosis (45%). Hospitalized patients presented more severe disease (P <0.001) and worst nutritional status defined by BMI (P =0.002), mid-upper arm circumference (P <0.001), mid-arm muscular circumference (P <0.001), triceps skinfold (P =0.07), and subjective global assessment (P<0.001). A third presented deficient/low handgrip strength. Alcohol consumption (P=0.03) and malnutrition detected by BMI (P =0.03), mid-upper arm circumference (P=0.001), triceps skinfold (P =0.06), mid-arm muscular circumference (P=0.02) were associated with CLD severity. The authors concluded that triceps skinfold is the most efficient anthropometric parameter and is associated with mortality.

A study by Teiusanu A et al. in 2012 [6] studied nutritional Status in Cirrhotic Patients. In a series of 176 hospitalized patients with cirrhosis, 114 (65%) males, median age 52 years, commonest etiology of liver disease was alcohol in 98 (56%) patients. Malnutrition was correlated with the severity of liver disease. The mild-moderate malnourished patients were 88% Child B, over 58% with viral etiology. 22% of these patients were alcoholics, and 11% had Child C score (p<0.01). In the severely malnourished group, 43% had the alcoholic disease, and 31% were Child C classification (p<0.01). Triceps skinfold thickness (mm) and mid-arm circumference(cm) decreased significantly according to the Child score; a positive correlation was found between Triceps skinfold and MAMC with the severity of cirrhosis.

Sarcopenia is seen in about 50% of the patients with liver cirrhosis and common among alcohol-related liver disease, ascites, and encephalopathy. The present study as well tried to evaluate these facts. Cirrhotic patients underwent abdominal computed tomography (CT) scan, including L3 and umbilical levels, to measure transverse psoas muscle thickness per height.

Sarcopenia was seen in 27/100(27%) patients in the present study population. The mean age of patients with sarcopenia was 52.7±9.8 years. In a South Korean study by Bae EJ et al. in 2017, the rate of sarcopenia increased with age (19.2%, 29.1%, and 42.3% among the 20–39, 40–64, and 65 and older age groups, respectively). In the 20–39 age group, the prevalence of sarcopenia was higher in men. In the 40–64 age group, the prevalence of sarcopenia was higher in women. The overall estimates of the prevalence of sarcopenia in the general population were 10% (95% CI: 8-12%) in men and 10% (95% CI: 8-13%) in women, respectively. The Sarcopenia prevalence in cirrhosis ranges from 30–70% in previous studies, depending on the diagnostic tools utilized and the severity of the liver disease, with a higher prevalence in men (61.6%) than in women (36%).

Sarcopenia is a well- recognized complication of cirrhosis, and in cases of NASH and NAFLD, it can contribute to accelerating liver fibrosis to cirrhosis [7]. In this study, the proportion of sarcopenia in patients with alcohol intake was 16(59.3%), in HBV+ patients was 2(7.4%), HCV+ patients were 3(11.1%), NASH related

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patients was 2(7.4%), and with unknown etiology patients was 4(14.8%). None of the patients with AIH had sarcopenia.

In our study, among patients with ascites, 21(77.8%) patients had sarcopenia. In patients without ascites, sarcopenia was seen in 6 (22.2%) patients. There was a significant association between the presence of ascites and sarcopenia with p=0.001.

In CTP class A, 4(14.8%) patients had sarcopenia. In CTP class B, sarcopenia was seen in 23(85.2%) patients. There was a significant association seen between Child-Turcotte-Pugh class and sarcopenia with p=0.001. In patients with a MELD score of

<15, sarcopenia was seen in 15(55.6%) patients, and 12(44.4%) patients had sarcopenia with MELD >15. There was a significant association seen between MELD score and sarcopenia with p = 0.026.

Despite certain advantages of the MELD and CTP scores, the major limitation of these scores is the lack of evaluation of the nutrition and functional status of patients with cirrhosis. However, estimation of the nutritional status in patients with cirrhosis is difficult because of fluid collection caused by impaired protein synthesis. Therefore, objective assessment of nutritional status needs to be established in cirrhotic patients.

The study by Durand et al [8] showed that the MELD-sarcopenia score, which combines MELD and psoas muscle area scores, is superior to that of the MELD score. These findings suggest that sarcopenia is an attractive prognostic factor to improve organ allocation in patients with cirrhosis. However, Tandon et al noted that the impact of sarcopenia was significant in patients with low MELD scores (<15; P = .02) but not in patients with higher MELD scores (<15; P = .59). These results are consistent with data from Merli et al, who demonstrated that muscle loss was predictive of mortality in CTP class A and CTP class B patients but not in patients with CTP class C cirrhosis. Taken together, these results suggest that further validation is needed. If validated, clinical trials are warranted to explore whether transplantation in sarcopenic patients with lower MELD scores may be superior.

Romagna ES et al in 2020, found no correlation between Child-Pugh and MELD severity scores, and presence of sarcopenia. Montano-Loza AJ et al, [9] studied 112 patients with cirrhosis who were consecutively evaluated for liver transplant and who had a CT scan at the third lumbar (L3) vertebrae were selected. Correlations between sarcopenia and MELD and CTP and between sarcopenia were studied. A poor correlation between sarcopenia and MELD score (r = 0.04, P .7) and Child–Pugh score (r = 0.01, P .9) was observed. Also, there was a poor correlation between sarcopenia and serum albumin (r = -0.02, P .9) and serum sodium (r = -0.11, P .2).

The handgrip strength was reduced in 27(100%) patients with sarcopenia [<27kg for men and < 16kg for women]. Handgrip strength was significantly associated with sarcopenia p=0.001. The ROC curve of handgrip strength for predicting sarcopenia had an area under the curve of 0.85 (excellent) with a cut-off of 27kg. It showed a sensitivity of 64% and a specificity of 100%.

The handgrip strength was reduced in 5(16.1%) patients of CTP class A and 26(83.9%) patients with CTP class B. There was a significant association between Child-Turcotte-Pugh class and handgrip strength in chronic liver disease patients with p=0.001. A significant correlation was seen between handgrip strength and MAMC, BMI, Gait Speed, and CT PMTH (p<0.05).

In a prospective study from North India, the authors showed that compared to MAMC, Handgrip strength showed the highest area under curve 0.82 (95% confidence interval (CI) 0.78–0.86, P = 0.001). The authors concluded that handgrip strength is an excellent tool to assess the nutrition status in patients with cirrhosis at the bedside and has the highest diagnostic accuracy than other anthropometric tests such as MAMC and TST.

We studied muscle performance in terms of Gait speed, and it was reduced in 18(66.7%) of patients with sarcopenia. Gait Speed was significantly associated with sarcopenia p=0.001. The ROC curve of gait speed for predicting sarcopenia had an area under the curve of 0.75 (acceptable) with a cut-off of 0.75 m/sec and showed a sensitivity of 89% and specificity of 67%.

Gait speed was reduced in 6(23.1%) patients of CTP class A and 20(76.9%) patients with CTP class B. There was a significant association between Child-Turcotte-

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Pugh class and gait speed in chronic liver disease patients with p=0.031. A significant correlation was seen between Gait speed and MELD score, MAMC, BMI, HGS, and CT PMTH (p<0.05).

4-m gait speed – duration <1 min - This test is one of the best predictors of disability, morbidity, mortality, and fall risk across various chronic diseases and the elderly [10]. It is recommended by the ACSM guidelines as a basic test of function before exercise initiation.1 In 373 patients with cirrhosis, gait speed was independently associated with hospitalization rate after adjusting for covariates such as MELD and Child-Pugh score. Mean gait speed was 0.95 m/s with every 0.1 m/s decreases in gait speed associated with a 22% increase of hospital day stay with significant projected cost implications. Gait speeds of less than 0.6 to less than 0.8 m/s have been associated with poor outcomes in older adults [11].

CT PMTH was reduced in 27(100%) of patients with Sarcopenia [Cut-off of PMTH <16.8 mm/m2 was taken for sarcopenia]. There was a significant association between psoas muscle thickness per height and sarcopenia with p=0.001. The ROC curve of psoas muscle thickness per height measured with CT for predicting sarcopenia had an area under the curve of 0.89 (excellent) with a cut-off of 16.52mm. It showed a sensitivity of 75% and a specificity of 100%.

PMTH was reduced in 9(20.5%) of CTP class A and 35(79.5%) with CTP class B. There was a significant association seen between Child-Turcotte-Pugh class and CT psoas muscle thickness per height in chronic liver disease patients with p=0.001. There was a significant correlation of CT PMTH with TSFT, BMI, HGS, and Gait Speed (p<0.05). We also found that muscle mass area measured through CT analysis correlated with the MAMC at anthropometry.

It is vital to measure the dimensions and surface area of the psoas major. It has the great advantage of being easily feasible because it does not require special software. Durand et al. [65] also found a significant association between transversal psoas muscle thickness normalized to height and mortality on the liver transplantation waiting list, independently of MELD. CT scan can identify the highest percentage of sarcopenia in cirrhosis. CT scan is the first technique that enables evaluation of the central muscle wasting, which might be less affected by sex, physical activity, and water retention. It is essential to recognize that the high cost, the possible limited access to the equipment, and the concern in terms of radiation exposure may limit the use of this technique for routine clinical practice unless the patient needs to perform a CT scan for other purposes.

A prospective observational study from South Korea in 2018 included 653 cirrhotic patients and studied the Clinical usefulness of psoas muscle thickness for the diagnosis of sarcopenia. The average age was 53.6 ± 10.2 years, and 499 patients (76.4%) were men. PMTH correlated well with SMI in both men and women (P<0.001). 241 (36.9%) patients met the criteria for SMI-sarcopenia. The best PMTH cut-off values for predicting SMI-sarcopenia were 17.3 mm/m in men and 10.4 mm/m in women, and these were defined as sex-specific cut-offs of PMTH (SsPMTH). Two hundred thirty (35.2%) patients were diagnosed with SsPMTH-sarcopenia, and 280 (44.4%) patients were diagnosed with SnPMTH-sarcopenia.

The present study corroborates with observations of previous studies that malnutrition is prevalent in patients with sarcopenia. There was a significant association seen between sarcopenia and Handgrip Strength, Gait Speed, and Psoas Muscle thickness per height measured with Computed Tomography. Sarcopenia represents an essential prognostic factor in cirrhotic patients and can assess the advanced liver disease. Hence, it is vital to study interventions to improve sarcopenia among cirrhotic patients in well-controlled studies.

CONCLUSION

Sarcopenia is prevalent in the studied cirrhotic patients causing limitation of activities and increases the risk of fall. It was more commonly seen in middle-aged men. The commonest etiology of cirrhosis in sarcopenia was alcohol. There was a significant association seen between sarcopenia and Handgrip Strength, Gait Speed, and Psoas Muscle thickness height measured with Computed Tomography. There was a significant association shown between Child-Turcotte-Pugh class (A and B) and sarcopenia in our study, suggesting these patients may need routine surveillanceudy and early treatment to prevent future risk.

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