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Sarcopenia in Patients with Liver Cirrhosis Assessed by Skeletal Muscle Ultrasound and Its Relation to Serum Testosterone Level

Amira K. El-Alfy[1], Basma Abd El aty Badr[1], Walid S. El-Din[2], Raof M. Rashed*[1], Mohamed Abd Ellatif Afifi[1]

Department of [1]Internal Medicine and [2]Rheumatology, Faculty of Medicine, Benha University, Egypt.

***Corresponding author:** Raof M. Rashed, **Mobile:** (+20) 01112066346, **Email:** raofrashed4@gmail.com

ABSTRACT

Background: When it comes to quantifying muscle mass in cirrhotic patients, Computed Tomography (CT) is the gold standard; nevertheless, CT is not practical for muscle measurement due to its high cost, radiation exposure, and logistical issues. Ultrasound detection of quadriceps muscle thickness has been recently presented as a more convenient bedside method to assess sarcopenia. The objective of the present study is to evaluate the role of ultrasound in assessment of biceps and quadriceps muscles thickness and echogenicity index as diagnostic parameters in liver cirrhosis patients and to study the relationship between sarcopenia and testosterone levels in these patients.

Patients and methods: A total of 50 cirrhotic patients were enrolled in this study from June 2021 to June 2022 at the Internal Medicine Department of Benha University Hospital. Our study included patients having diagnostic evidence of advanced liver cirrhosis (clinical, laboratory, and/or ultrasonographic) and aged >18 years.

Results: Testosterone in men was found to have a favorable and statistically significant relationship with handgrip ($r = 0.667$, $P < 0.001$). In contrast, it showed significant negative correlations with rectus femoris echo index ($r = -0.459$, $P = 0.008$) and F-SARC ($r = -0.766$, $P < 0.001$). Non-significant correlations were reported between testosterone and biceps echo index ($P = 0.523$), biceps thickness ($P = 0.340$), and rectus femoris thickness ($P = 0.185$).

Conclusion: The thickness and echogenicity index of muscle is a reliable index for gauging muscle wasting in cirrhotic individuals. Sarcopenia can be evaluated with ultrasound, which might make it possible to track patients' nutritional condition over time.

Keywords: Sarcopenia, Skeletal ultrasound, Testosterone, Liver cirrhosis.

INTRODUCTION

It is becoming more and more apparent that sarcopenia, or the wasting away of muscular mass and function, is a common consequence of advanced cirrhosis that is linked to poor clinical outcomes. Sarcopenia in patients with advanced liver illness has been the subject of numerous studies recently, although there is still no agreed-upon "optimal method" for making the diagnosis. Other fields, such as geriatrics, from which many diagnostic techniques are derived, also struggle to establish a definitive "gold standard" [(1)].

Disagreements about how to diagnose sarcopenia are slowing down efforts to design clinical trials to identify effective treatments for the condition and have serious consequences for the quality and reproducibility of cohort research in the field. We still don't know much about the pathophysiology of sarcopenia in cirrhosis, the mechanisms by which it affects patient outcomes, the diversity of patient populations, and the reliability, accessibility, and affordability of tests that measure muscle mass and function, all of which contribute to the difficulty of making a diagnosis [(2)].

The association between sarcopenia and worse outcomes in cirrhotic individuals is now extensively documented in the hepatology literatures. Clinically significant sarcopenia appears to be more prevalent in males than females with cirrhosis. yet the mortality (50 percent increase in waitlist mortality) and dropping out of the liver transplant waitlist in both sexes have been strongly linked to higher functional metrics assessing frailty [(3)].

Many studies of cirrhotic patients awaiting liver transplantation report a prevalence of sarcopenia nearing 70%; however, the actual number might range greatly depending on the diagnostic method used, the study population, and the gender of the patients [(4)].

The prevalence of sarcopenia is lower in individuals with NAFLD compared to patients with other disease etiologies, but the prevalence of frailty is higher; this may be due to a relative rather than absolute deficiency of muscle mass in relation to fat mass [(5)]. Despite being the current gold standard for quantifying muscle mass in cirrhotic patients, Computed Tomography (CT) is not practical for muscle evaluation because of its high cost, high radiation exposure, and logistical issues. Ultrasound detection of quadriceps muscle thickness has been recently presented as a more convenient bedside method to assess sarcopenia [(6)].

Metabolic problems, inadequate nutrition, malabsorption, reduced liver ability to metabolize, and endocrine abnormalities are major factors to muscle atrophy in cirrhosis. In populations with renal failure, heart failure, and chronic obstructive pulmonary disease, reduced testosterone levels have been linked to the development of sarcopenia. Testosterone levels in men with cirrhosis are lower than in healthy controls because of a combination of factors, including hypothalamic-pituitary dysfunction, peripheral aromatization of androgens, and gonad failure. The loss of adipose tissue in female individuals with Cirrhosis is more likely to happen before the loss of

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muscle tissue. In cirrhosis, low testosterone levels are a significant risk factor for death [7].

The objective of the present study is to evaluate the role of ultrasound in assessment of biceps and quadriceps muscles thickness and echogenicity index as diagnostic parameters in liver cirrhosis patients and to study the relationship between sarcopenia and testosterone levels in these patients.

PATIENTS AND METHODS

A total of 50 cirrhotic patients were included in this study between June 2021 and June 2022 at the Internal Medicine Department of Benha University Hospital. Patients older than 18 years old who had clinical, laboratory, and ultrasonographic evidence of liver cirrhosis were included in the study.

Patients on hormone replacement treatment of any kind, those with extrahepatic malignancy, renal failure needing dialysis, chronic lung disease necessitating supplemental oxygen, and congestive heart failure with an ejection fraction of less than 40% were not eligible to participate.

Biochemical investigations, including liver function tests, were performed on all patients after a thorough history and physical examination for signs of liver cirrhosis.; complete blood count (CBC), markers of liver injury: alanine amino transferase (ALT), liver function tests: serum bilirubin (total, direct), serum albumin, aspartate amino transferase (AST),prothrombin time and International normalized ratio (INR), anti-hepatitis C virus antibodies (HCV-Ab) and hepatitis B surface antigen are viral indicators (HBsAg), serum alpha fetoprotein (AFP), and serum testosterone level measured with an electrochemiluminescence immunoassay (ECLIA), Biceps and Quadriceps muscle thickness measured by ultrasound and Echogenicity index measured by Photoshop grayscale analysis. Patients were classified according to Child-Pauh scoring system [8].

Inclusion criteria:

Patients must be between the ages of 18 and 80, have a histologically or cytologically (nodules of regeneration are present), radiological (cross-sectional imaging or ultrasound revealing hepatic lobulation and/or blatant evidence of portal hypertension) or a temporary elastography test (where liver stiffness is measured if it's greater than 14 kPa).

Exclusion criteria: Patients with extrahepatic malignancy, ESRD requiring dialysis, COPD requiring oxygen supplementation, cardiac failure with an ejection fraction 40%, or any form of hormonal replacement therapy.

Methods:

For all studied cases the following will be done: Comprehensive physical assessment, extensive medical history gathering, Liver function tests (AST, ALT, serum albumin, serum bilirubin, and prothrombin time), complete blood count, and other laboratory tests, INR Alpha fetoprotein, Serum testosterone level measured with an electrochemiluminescence immunoassay (ECLIA), HCV Ab and HBS Ag, Abdominal ultrasound, Skeletal muscle ultrasound: Ultrasound on the biceps and rectus femoris muscle to measure thickness and to analyze the echogenicity index using adobe photoshop, Hand grip strength: Hand grip strength of the dominant hand was tested by hand dynamometer that is using the unit of scale: Kg, Functional grading: Using the SARC-F questionnaire to grade the muscle function as in table 1 [9].

Table (1): SARC- F questionnaire of muscle function [9].

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 lb?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen	None = 0

Skeletal muscle thickness and echogenicity index will be examined statistically to determine their usefulness in assessing muscle atrophy in cirrhotic individuals. Sarcopenia can be evaluated with ultrasound, which might make it possible to track patients' nutritional condition over time.

Ethical consent:

An approval of the study was obtained from the Institutional Review Board at the Banha University School of Medicine. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 25 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The Kolmogorov-Smirnov test, the Shapiro-Wilk test, and direct data visualization were utilized to check the normality of the quantitative data. Means and standard deviations or medians and ranges were calculated from numerical data in accordance with the assumption of normalcy.

Numerical and percentage summaries of the categorized data were generated. The independent t-test or the Mann-Whitney U test was used to compare quantitative data based on Child score, depending on whether the variables were normally or non-normally distributed. Spearman's correlation was used to find associations between testosterone and the other variables. Child B&C patients were differentiated using ROC analyses of biceps thickness, F-SARC, and handgrip. Each variable's Area under Curve (AUC) and 95% CI, optimal cutoff point, and diagnostic indices were determined. Statistical analyses were always performed on a binary outcome. P value $\leq$0.05 was considered significant.

RESULTS

Skeletal US findings

The mean biceps echo index was 17.15 (SD 3.15), while the mean thickness was 1.61 (SD 0.54). Regarding the rectus femoris, the mean echo index was 12.91 (SD 2.63), while the mean thickness was 1.36 (SD 0.16) **(Table 2, Figure1)**.

Table (2): Skeletal US findings in the studied patients.

Variable	Mean ± SD
Biceps	
Echo index	17.15 ± 3.15
Thickness	1.61 ± 0.54
Rectus femoris	
Echo index	12.91 ± 2.63
Thickness	1.36 ± 0.16

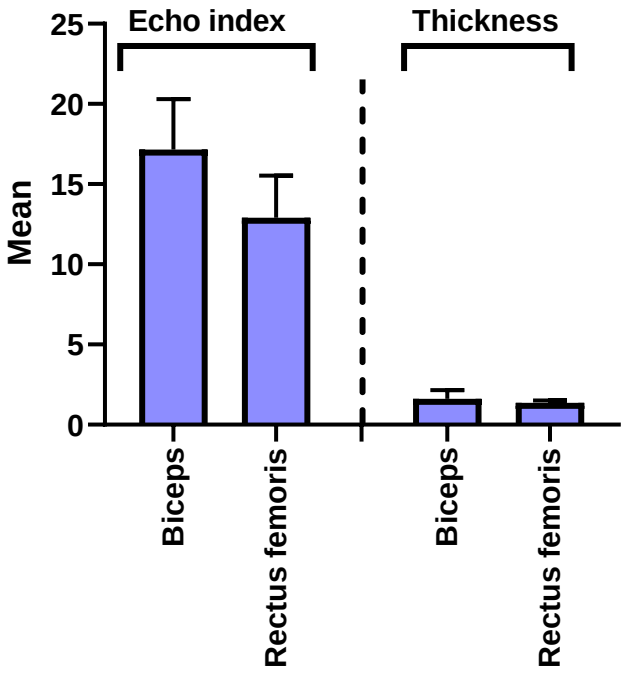

Figure (1): Skeletal US findings in the studied patients.

Correlation between testosterone and other parameters in males

Testosterone in men was found to have a favorable and statistically significant relationship with handgrip.(r = 0.667, P <0.001). In contrast, it showed significant negative correlations with rectus femoris echo index (r = -0.459, P = 0.008) and F-SARC (r = -0.766, P <0.001) **(Table 3, Figures 2, 3)**. No significant correaltions were reported between testosterone and biceps echo index (P = 0.523), biceps thickness (P = 0.340), and rectus femoris thickness (P = 0.185) **(Table 3)**.

Table (3): Correlation between testosterone and other parameters in males

Variable	Testosterone (pg/ml)	
	R	P-value
Biceps echo index	0.117	0.523
Biceps thickness	0.174	0.340
Rectus femoris echo index	-0.459	0.008*
Rectus femoris thickness	-0.240	0.185
F-SARC	-0.766	< 0.001*
Handgrip (kg)	0.677	< 0.001*

r: Correlation coefficient; * Significant

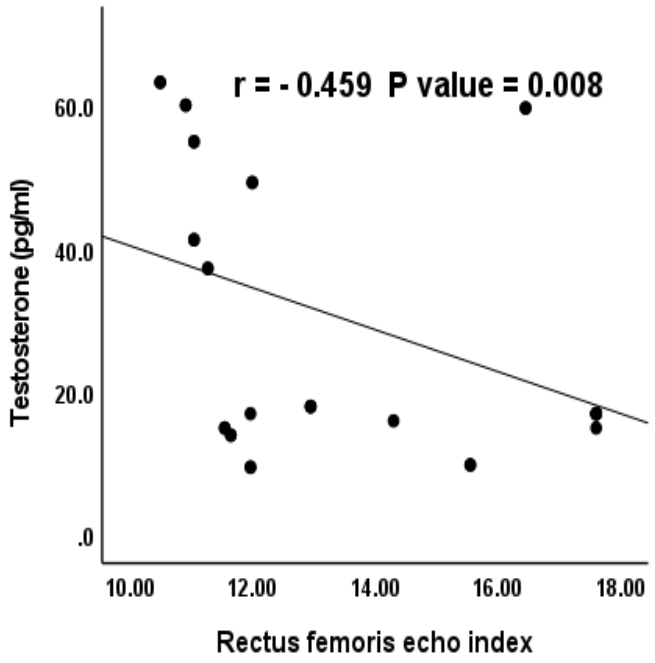

Figure (2): Correlation between testosterone and rectus femoris echo index

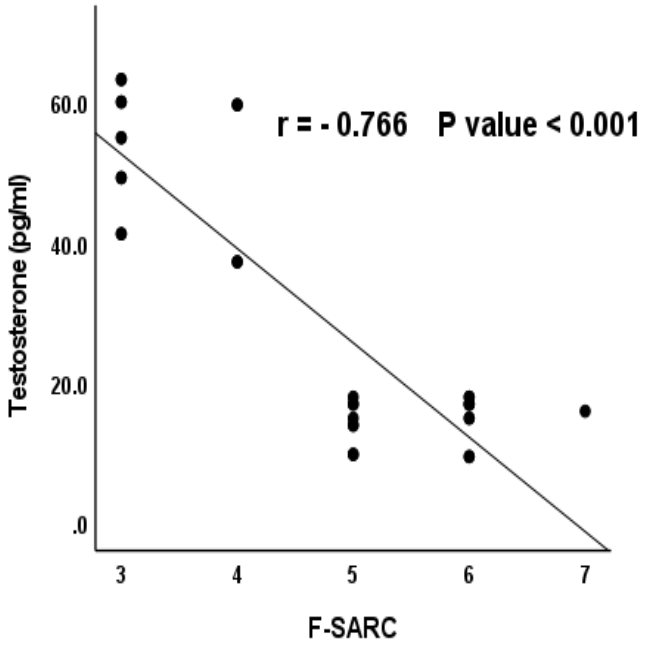

Figure (3): Correlation between testosterone and F-SARC

Correlation between testosterone and other parameters in females

No significant correlations were reported between testosterone in females and biceps echo indies (P = 0.892), biceps thickness (P = 0.682), rectus femoris echo index (P = 0.740), rectus femoris thickness (P = 0.07), F-SARC (P = 0.078), and handgrip (P = 0.541) **(Table 4).**

Table (4): Correlation between testosterone and other parameters in females

Variable	Testosterone (pg/ml)	
	R	P-value
Biceps echo index	-0.035	0.892
Biceps thickness	-0.104	0.682
Rectus femoris echo index	-0.084	0.740
Rectus femoris thickness	0.436	0.07
F-SARC	-0.426	0.078
Handgrip (kg)	0.154	0.541

r: Correlation coefficient; * Significant

Different indices according to Child score

The most frequent child score was A (54%), followed by B (40%) and C (6%).Biceps thickness was significantly higher in those with Child A (1.75 ±0.59) than in those with Child B&C (1.44 ±0.43) (P = 0.037). In addition, those who had Child B&C had a much higher F-SARC (median = 6, range = 5-7) than in those with Child A (median = 4, range = 3-5) (P < 0.001). Furthermore, those that had a Child A had noticeably stronger handgrips (34 ±12) than in those with Child B&C (24 ±5) (P < 0.001) **(Table 5, Figures 4 and 5)**.

No significant differences were detected regarding biceps echo index (P = 0.219), rectus femoris echo index (P = 0.406), and rectus femoris thickness (P = 0.772) **(Table 5)**.

Table (5): Different indices according to Child score

Variable	CHILD.COM		
	A	B & C	P-value
Biceps echo index	17.66 ±3.25	16.55 ± 3	0.219
Biceps thickness	1.75 ± 0.59	1.44 ± 0.43	0.037*
Rectus femoris echo index	12.62 ± 2.49	13.25 ± 2.82	0.406
Rectus femoris thickness	1.35 ± 0.15	1.36 ± 0.17	0.772
F-SARC	4 (3 - 5)	6 (5 - 7)	<0.001*
Hand grip (kg)	34 ± 12	24 ± 5	<0.001*

Data were presented as mean ± SD or median (min-max); *significant

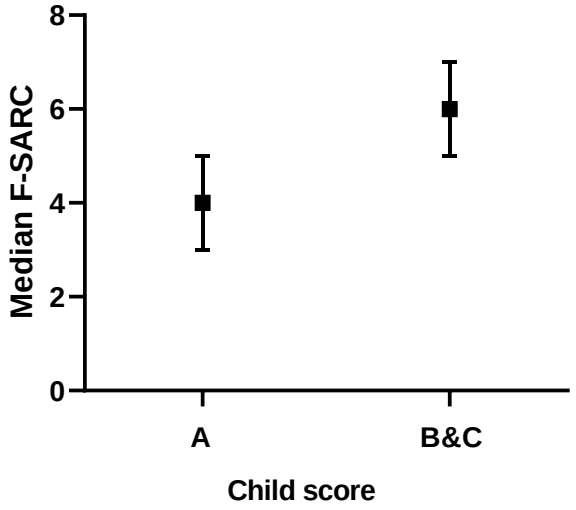

Figure (4): F-SARC according to Child score

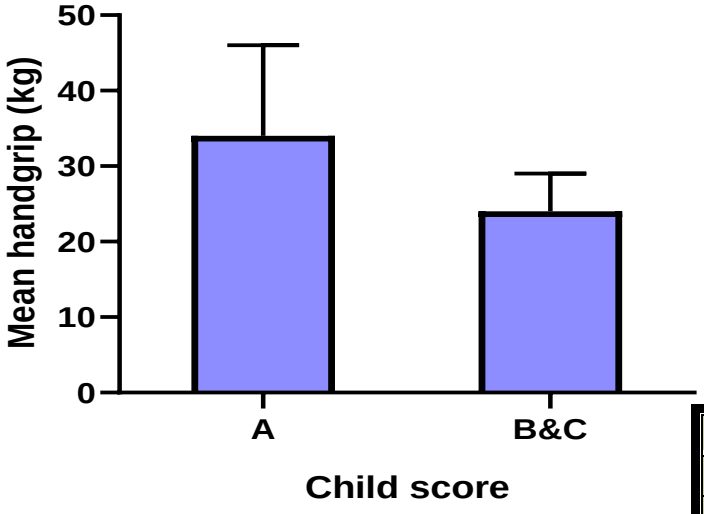

Figure (5): Handgrip according to Child score of the studied groups.

ROC analysis of biceps thickness for distinguishing Child B&C patients

ROC analysis was done for biceps thickness to distinguish Child B&C patients. It revealed a significant area under curve of 0.7 (P = 0.016) with a 95% confidence interval ranging from 0.551 – 0.849. The best cutoff was ≤ 1.75, at which sensitivity and specificity were 91.3% and 59.3%, respectively **(Table 6, Figure 6)**.

Table (6): ROC analysis of biceps thickness for distinguishing Child B&C patients

ROC characteristics	
AUC (95% CI)	0.7 (0.551 - 0.849)
Best cutoff	≤1.75
Sensitivity	91.3%
Specificity	59.3%
P-value	0.016

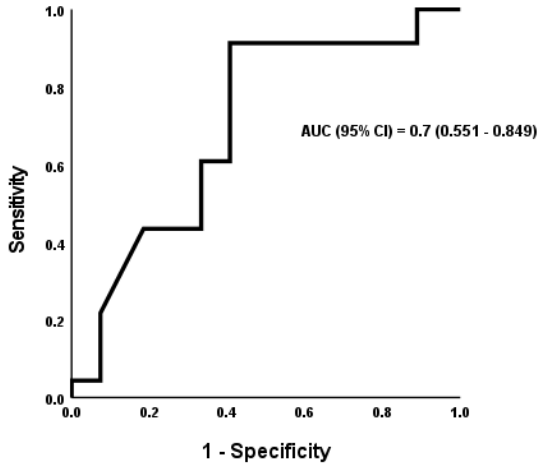

Figure (6): ROC curve of biceps thickness for distinguishing Child B&C patients

ROC analysis of F-SARC for distinguishing Child B&C patients

ROC analysis was done for F-SARC to distinguish Child B&C patients. It revealed a significant area under curve of 0.976 (P < 0.001) with a 95% confidence interval ranging between 0.941 – 1.0. The best cutoff was > 4, at which sensitivity and specificity were 100% and 88.9%, respectively **(Table 7, Figure 7)**.

Table (7): ROC analysis of F-SARC for distinguishing Child B&C patients

ROC characteristics	
AUC (95% CI)	0.976 (0.941 - 1.0)
Best cutoff	>4
Sensitivity	100%
Specificity	88.9%
P-value	<0.001

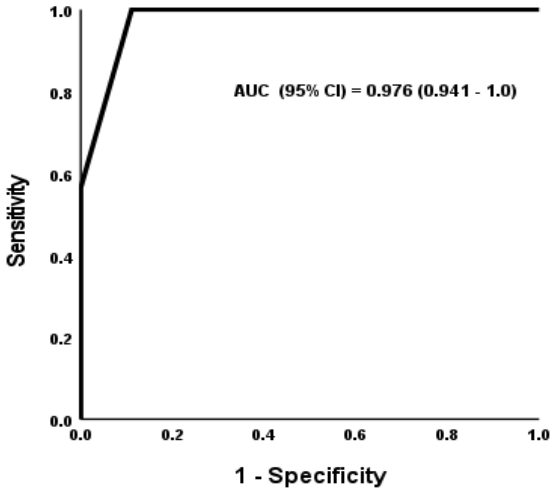

Figure (7): ROC curve of F-SARC for distinguishing Child B&C patients

ROC analysis of handgrip for distinguishing Child B&C patients

ROC analysis was done for handgrip to distinguish Child B&C patients. It revealed a significant area under curve of 0.715 (P = 0.009) with a 95% confidence interval ranging between 0.572 – 0.858. The best cutoff was ≤ 30, at which sensitivity and specificity were 100% and 51.9%, respectively **(Table 8, Figure 8)**.

Table (8): ROC analysis of handgrip for distinguishing Child B&C patients

ROC characteristics	
AUC (95% CI)	0.715 (0.572 - 0.858)
Best cutoff	≤30
Sensitivity	100%
Specificity	51.9%
P-value	0.009

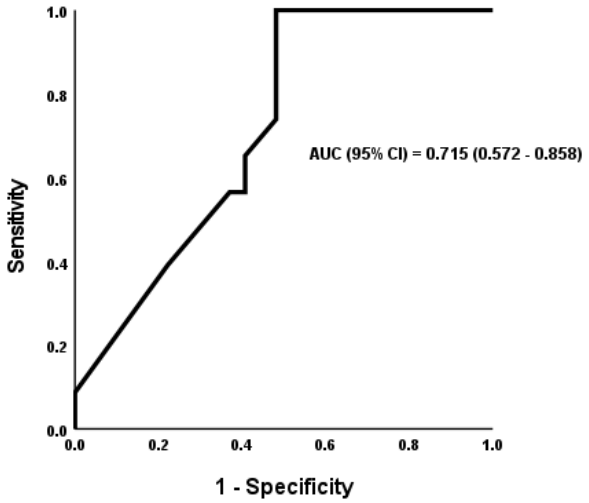

Figure (8): ROC curve of handgrip for distinguishing Child B&C patients

DISCUSSION

The decline in skeletal muscle mass is an important part of the diagnostic process for sarcopenia in the elderly. A precise measurement of skeletal muscle mass loss (both quantitatively and qualitatively) is essential for the diagnosis of sarcopenia, despite the growing recognition of the necessity of associating functional measures that were to evaluate the loss of muscle performance in the aged [(10)]. Therefore, it is suggested that these two metrics be assessed together during the measurement of muscle mass. Dual energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) are examples of diagnostic tools that can only provide quantitative data regarding skeletal muscle structure, while CT and magnetic resonance imaging (MRI) can provide a more comprehensive picture but are limited in their application to routine clinical work. Because of its high correlation with MRI, CT, and DXA for evaluating skeletal muscle mass and its ability to provide both quantitative and qualitative data, ultrasound imaging of the skeletal muscle provides a viable alternative [(11)].

Although additional research on the standardization of ultrasonic measurement methods is required, the SARCUS study has offered the first step in this regard (SARCopenia through Ultrasound) [(12)].

Ultrasonography (US) has a considerable degree of connection with DXA in muscle studies and can efficiently evaluate the number and quality of muscle tissue. Muscle thickness (MT), cross-sectional area (CSA), and volume (MV) are a few of the ultrasound characteristics that can be used to assess muscle mass (MT). The muscle can also be described qualitatively using other metrics such as echo intensity (EI), pennation angle (PA), fascicle length (FL), and physiologic cross-sectional area (PCSA). The measuring of vascularity is one such experimental method [(13)].

Although a number of different "regional sites" might be employed to investigate these parameters, the anterior thigh compartment is by far the most common. Furthermore, sarcopenia often manifests in only one area. The region in question has a very high rate of lower-body muscle atrophy [(11)].

With a test-retest correlation of 0.98 to 0.99 and a correlation with MRI of 0.99, ultrasound of the muscles is an accurate method for determining muscle thickness and cross-sectional areas. Ultrasound has been employed in multiple research investigations to assess muscle thickness in healthy participants. Muscle thickness rises in both sexes after puberty, reaching a maximum between the ages of 25 and 50. After that point, muscular atrophy sets in. Considering a patient's age and gender when analyzing their muscle ultrasound scan is important.

The purpose of this study was to provide evidence linking testosterone levels to sarcopenia as measured by ultrasonography of the skeletal muscles. Age, liver disease stage, and cirrhosis cause were not involved in this correlation.

US can assess muscle anatomy by measuring the muscle's echogenicity. Typical musculature has a dark color. The acoustic impedance of fatty tissue and that of fibrous tissue is different. As a result, there are more muscle surfaces that reflect light, making the muscle look whiter. Variations in the amount of fibrous tissue and the orientation of muscle fibres give different muscles their own distinctive looks on ultrasound [(13)].

The echogenicity of muscle tissue tends to rise with age. This is because as we become older, our bodies naturally replace our working muscles with fat and fibrous tissue. This similar process also contributes to elevated muscle echogenicity in liver cirrhosis. It might be challenging to visually detect even a little increase in muscle echogenicity. The

observer's skill plays a large role in making an accurate assessment. This is because the echogenicity of muscles changes over time and the appearance of individual muscles varies. Also, altering the US machine's settings, such turning up the gain, might make muscles look whiter, which could be misinterpreted as pathologically heightened echogenicity. These factors contribute to the low inter-observer agreement seen in muscle US (Kappa = 0.53), which is further reduced when an unskilled observer evaluates the images [(14)].

To get around these issues, simple grey scale analysis performed with the aid of a computer was used to quantify muscle echogenicity. Interobserver agreement is quite high for the clinical technique of quantitative examination of muscle echogenicity (Kappa 0.86). It's good for conducting experiments of this sort.

Our study showed that, there was a correlation between skeletal muscle thickness and Echo index assessed by ultrasound, the muscle strength and function represented by the F- SARC questionnaire and the hand grip. There was also a correlation between skeletal muscle thickness and state of liver cirrhosis according to Child score but this correlation was biased by other factors contributing to sarcopenia other than liver state like the etiology of liver disease, the age of the patient, the nutritional state of the patient and the life style of the patient including physical exercise.

Sarcopenia in cirrhosis has been linked to low testosterone levels among other factors [(14)]. While we did find that testosterone was significantly lower in male patients with sarcopenia, the correlation between testosterone and skeletal muscle thickness was weak, suggesting that many factors are involved in sarcopenia and that the severity of hypotestosteronemia is not directly related to the severity of muscle wasting. The results of these investigations align with those of more recent ones by **Sinclair *et al.*** [(4)] study showed low testosterone levels were related with greater mortality in male patients with cirrhosis and that there was a weak but significant connection between testosterone levels and muscle mass.

In addition, we employed an immunoassay to measure testosterone levels, which is less sensitive in female patients due to their naturally lower testosterone concentrations compared to men. This further confounds our ability to draw firm conclusions from our findings in this demographic. Sarcopenia and low testosterone levels in women: a connection that needs more research.

Because of the complexity of the underlying causes, no one medication is likely to be effective in treating sarcopenia in liver cirrhosis. In an effort to combat the anabolic resistance that characterizes cirrhosis, current treatment strategies have concentrated on nutritional supplements, essentially just replacing calories and proteins through various methods of administration. Although this demographic may benefit from exercise and other forms of physical activity, exhaustion makes it difficult to do so [(14)].

The evidence from supplementation trials in cirrhosis, as well as the strong correlation between sarcopenia and testosterone suggest that replacement treatment may be an effective therapeutic method for increasing muscle mass. Cirrhosis patients may benefit greatly from testosterone because of its potential to reduce the risk of fractures in this population [(15)].

More research on testosterone replacement therapy for cirrhosis is needed to validate the effect of supplementation on muscle mass and quality, determine whether there is a role for testosterone supplementation in female patients, and examine the safety of such intervention. Testosterone supplementation has been linked to a number of possible side effects. Hepatocellular carcinoma and testosterone levels have been associated in observational studies, however the results have been mixed [(16)].

Our research is not without flaws. A preliminary step is to evaluate testosterone's impact on sarcopenia. Ultrasound measurements of muscle thickness and echogenicity index were also used to estimate muscle mass.

Although we have demonstrated a correlation between testosterone levels and sarcopenia in male patients, we are unable to draw any causal inferences without a controlled experimental design.

Hormones including estrone, estradiol, prolactin, and free testosterone, which may all play a role in this correlation, were not measured. In reality, several research have shown conflicting results about whether free testosterone or total testosterone levels should be assessed in these individuals, and some studies have suggested that estrone and the testosterone/estradiol ratio might also have clinical and prognostic relevance.

Since female patients typically have lower testosterone levels, the sensitivity of immunoassays is often questioned by experts. Our assay, however, has been proven to agree well with liquid chromatography-mass spectrometry.

The lack of a standard range for measuring muscle thickness and echo index, as well as any information regarding the optimal ultrasonic settings that can produce varied thickness and echo index readings, is another constraint.

In conclusion, the thickness and echogenicity index of muscle is a reliable index for gauging muscle wasting in cirrhotic individuals. Sarcopenia can be evaluated with ultrasound, which might make it possible to track patients' nutritional condition over time. There is direct correlation between functional muscle state and muscle thickness and echo index assessed by ultrasound which would after future studies would

make it a gold standard and easy test for following up the muscle state in sarcopenic patients with liver cirrhosis. Correlation of testosterone level with sarcopenia is still questionable and needs future studies. The difference in levels between males and females and the effect of other hormones on the muscle state need future studies to fulfill the correlation with testosterone.

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Author contribution: Authors contributed equally in the study.

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