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***Prospective Study***

**Tongue thickness in health *vs* cirrhosis of liver: Prospective observational study**

Tandon M *et al*. Tongue thickness in health *vs* cirrhosis

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**Abstract**

BACKGROUND

Malnutrition affects 40%-90% of patients with cirrhosis of liver. L3 skeletal muscle index (L3SMI) is presently accepted as the most objective and quantitative measure available for sarcopenia, a surrogate marker of malnutrition. L3SMI application is, however, limited by non-availability of computed tomography scan in remote areas, cost, need for extensive training, and due to risk of exposure to radiation. An alternative dependable measure with wider availability is therefore needed. Malnutrition causes sarcopenia not only in the skeletal muscles but also in other muscular structures like psoas muscle, diaphragm and tongue. We therefore hypothesised that tongue, being easily accessible for inspection and for measurement of thickness using ultrasonography, may be used to document sarcopenia.

AIM

To measure and compare tongue thickness in healthy individuals and in patients with cirrhosis of liver and to study its correlation with conventional prognostic scores for patients with cirrhosis of liver.

METHODS

Tongue thickness was measured using ultrasonography. One hundred twenty subjects of either gender and of age 18 to 65 years were studied, with 30 subjects in each group. The tongue thickness was compared between groups based on “Child Turcotte Pugh” (CTP) scores. Correlation was also explored between measured tongue thickness and “Model for end stage liver disease” (MELD) score and between age and measured tongue thickness.

RESULTS

Mean tongue thickness (mean ± SD) for patients with CTP class A, B and C was 4.39 ± 0.39 cm, 4.19 ± 0.53 cm, and 3.87 ± 0.42, respectively, and was 4.33 ± 0.49 cm for normal healthy individuals. Significant difference was seen in tongue thickness between patients of CTP class C and those of CTP class A and B (*P* < 0.05). Patients of CTP class C also had significantly reduced tongue thickness than normal individuals (*P* < 0.05). However, no significant difference was seen in tongue thickness between patients of CTP class A and B and normal individuals. Statistically significant, negative correlation was found between MELD score and tongue thickness (R = -0.331) (*P* < 0.001). No correlation was seen between L3SMI and MELD score (R = 0.074, *P* = 0.424). L3SMI (mean ± SD) in healthy subjects was 39.66 ± 6.8 and in patients of child class C was 38.26 ± 8.88, and the difference was not significant. No significant correlation was found between age of the patients and tongue thickness. Intra-class correlation coefficient was used to determine the reliability of the tongue thickness measurements. The Intra-class correlation coefficient value was 0.984 (95%CI: 0.979-0.989) and was indicative of good reliability.

CONCLUSION

Tongue thickness measured by ultrasonography, correlates significantly with severity of liver disease, as assessed by CTP and MELD scores. The patients with CTP score ≥ 10 have significantly reduced tongue thickness as compared to normal individuals and those with less severe liver disease with CTP score of 5-9. No significant difference in tongue thickness was found between healthy individuals and CTP class A and B patients.

**Key words:** Sarcopenia; Malnutrition; Cirrhosis of liver; Child Turcotte Pugh class; Model for end stage liver disease score; Ultrasonography

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**Core tip:** Sarcopenia has implications for management and outcome of patients with cirrhosis of liver and therefore is considered for prognostication. However only objective and reproducible measure for sarcopenia is computed tomography (CT) scan measured skeletal muscle thickness, L3 skeletal muscle index (L3SMI). Application of L3SMI is however restricted by need for CT scan. Compared to CT scan measured L3SMI, tongue thickness can easily be measured in reproducible manner and accurately with minimal training using ultrasonography and as suggested by this study, is a more sensitive indicator of sarcopenia. Authors suggest wider studies to validate the findings and propose Tongue thickness as a tool to diagnose sarcopenia.

**INTRODUCTION**

Malnutrition has been estimated to affect 50%-90% of patients with cirrhosis of liver[1]. Malnutrition is, however, frequently overlooked, in part because nutritional assessment can be a difficult task in patients with cirrhosis due to fluid retention and also because patients with cirrhosis may develop simultaneous loss of skeletal muscle and gain of adipose tissue, culminating in the condition of “sarcopenic obesity”[1]. Sarcopenia is characterised by loss of the muscle mass and is a surrogate marker of malnutrition[2]. Severity of liver disease is assessed using “Model for end stage liver disease” (MELD) score, which is calculated with online calculator using values for serum creatinine, bilirubin and international normalised value for prothrombin time. MELD score is also used to decide upon organ allocation for liver transplant[3], and currently it does not include a measure of sarcopenia. Researchers have been suggesting changes in MELD score calculation to include a measure of sarcopenia, considering its prognostic implications[4]. Similarly, the “Child Turcotte Pugh” (CTP) score, a conventional scoring system for severity of liver disease based on values of serum bilirubin, albumin, international normalised value for prothrombin time, and measures of encephalopathy and ascites, does not include any measure of sarcopenia[5]. L3 skeletal muscle index (L3SMI) is presently accepted as the most objective and quantitative measure of sarcopenia[6]. However, non-availability of computed tomography (CT) scan in remote areas, cost, and exposure to radiation are limitations to the use of L3SMI; besides, use of CT scan for documenting and quantifying sarcopenia can be justified only in patients who have an indication for CT scan as part of their standard medical care due to risks of radiation exposure. An optimal index for sarcopenia in terms of availability, reproducibility, practicality, and of prognostic significance is therefore needed and remains a challenging issue.

Malnutrition causes sarcopenia in several muscular structures besides the much-studied lumbar muscles, like the diaphragm, psoas muscle and tongue[7-9]. In the quest to look for ultrasonography (USG) based, bed side targets for documenting sarcopenia, authors hypothesised that tongue being a muscular structure affected by sarcopenia and being easily accessible for inspection and measurement, may also be used to quantify and document sarcopenia. A prospective study was therefore conducted with the primary objective to measure and compare tongue thickness in healthy individuals and in patients with cirrhosis of liver and with the secondary objective to study its correlation with conventional prognostic scores for patients with cirrhosis of liver.

**MATERIALS AND METHODS**

The study was done at a tertiary care institute after approval by the institutional ethics committee. Consent for the study protocol was obtained from the study subjects. To study 30% difference with power of 80 and type II error of 5%, we needed to study 30 subjects in each group. A total of 120 subjects, sequentially satisfying inclusion criteria were enrolled and were studied between May 2017 to October 2018.

Patients with cirrhosis of liver of any aetiology and healthy individuals of age 18-65 years and body mass index (BMI) > 18 and < 30, visiting hospital for reason other than illness, were included in the study. Individuals of age less than 18 years and more than 65 years, patients of acute liver failure and subjects with glossitis were not included in the study. Tongue thickness was measured using ultrasonography with a 3.75 MHz convex probe while the subjects were seated in an upright position. Subjects were instructed to swallow their saliva several times to set the tongue at the resting position, following which ultrasonic measurements were carried out. The measurement points were determined on the upper and lower surfaces of the lingual muscles in the centre of the plane, perpendicular to the ‘Frankfurt horizontal plane’ in a frontal section (Figure 1). Frankfurt horizontal plane is formed by drawing a straight horizontal line from the top of the ear canal to the bottom border of the eye along either side of the human skull. The line is called a Frankfurt horizontal line[10]. The vertical distance was measured from the surface of the mylohyoid muscle to the tongue dorsum (Figure 2). Measurements were performed thrice in freeze-frame when the tongue was restored to the resting position after swallowing saliva, and the mean values were obtained. Tongue thickness was measured for all the study subjects, but the L3SMI was calculated from CT scans for only the Child C class of patients who were being investigated for liver transplant and for healthy individuals who were evaluated as possible organ donors. MELD scores were calculated using online calculator at the website <https://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older>. The tongue thickness was compared between groups based on CTP scores. Correlation was also explored between measured tongue thickness and MELD score, and between age and measured tongue thickness.

***Statistical analysis***

Data was presented as mean ± SD or in frequencies (Percentage) and was analysed by SPSS 23.0 software. One-way ANOVA was used to test significance for parametric data and Kruskalwali’s test for non parametric data. Comparison of categorical data was done using chi square test/Fisher’s exact test. The continuous data was compared by student *t*-test/Mann-whitney test, as applicable. *P* value less than 0.05 was considered significant. Intra-class correlation coefficient (ICC) was used to determine the reliability and agreement amongst the tongue thickness measurements.

**RESULTS**

Out of 120 patients, 96 were males and 24 were females. Mean age was 47.12 years. The various aetiologies for cirrhosis were Ethanol-related, Non-alcoholic steato-hepatitis, cryptogenic, Hepatitis B Virus, Hepatitis C Virus, Autoimmune, Hepatic vein outflow tract obstruction, Non-alcoholic fatty liver disease, and Primary sclerosing cholangitis (Figure 3).

***Tongue thickness and CTP score***

Mean tongue thickness for patients with CTP class A was 4.39 ± 0.39 cm (Range 4.25-4.53), for patients of CTP class B was 4.19 ± 0.53cm (Range 3.99-4.39), for patients of CTP class C was 3.87 ± 0.42 (Range 3.71- 4.02) and for normal healthy individuals was 4.33 ± 0.49 cm (Range 4.15-4.51) (Table 1; Figure 4).

Significant difference was seen in tongue thickness between patients of CTP class C and those of CTP class A and B (*P* < 0.05). Patients of CTP class C also had significantly reduced tongue thickness than normal individuals (*P* < 0.05). However, no significant difference was seen in tongue thickness between patients of CTP class A and B and normal individuals (Table 2).

***MELD score***

Mean (± SD) MELD score for patients of child class A, B and C was 9.63 ± 2.24, 13.90 ± 2.96 and 25.37 ± 7.92, respectively.

***Tongue thickness and MELD score***

Statistically significant, negative correlation was found between MELD score and tongue thickness (*R*: −0.331) (*P* < 0.001) (Table 3).

***Age and Tongue thickness***

No significant correlation was found between age of the patients and tongue thickness by USG (Table 4).

***Tongue thickness and L3SMI***

No significant correlation was found between tongue thickness and L3SMI (*P* = 0.83). (Table 5). For L3SMI in healthy subjects, mean (± SD) value was 39.66 ± 6.8, and was 38.26 ± 8.88 in patients of child class C. The difference was not significant(*P* = 0.63) (Table 6). Barring the outliers, 2 each in healthy subjects and in Child C patients, the median L3SMI was 40.19 (33.89-45.4) in healthy subjects while it was 39.39 (32.68-45.35) in Child C patients (Figure 5). ICC was used to determine the reliability of the tongue thickness measurements. The ICC value was 0.984 (95%CI: 0.979-0.989) and is indicative of good reliability (Table 7).

**DISCUSSION**

Our study indicates that tongue thickness measurement by USG correlates significantly with severity of liver disease, as assessed by CTP scores. The study establishes that patients with CTP score ≥ 10 have significantly reduced tongue thickness as compared to normal individuals and those with less severe liver disease with CTP score of 5-9. Studies have shown that sarcopenia also affects other muscles besides the much studied L3SMI[7-9]. Tongue thickness has even been explored as a bed side measure of sarcopenia in patients with critical illness and has also been correlated with clinical outcome[9].

Malnutrition in cirrhosis is secondary to a multifactorial process and is seen more often in patients with more severe liver disease. We studied correlation of tongue thickness with the MELD score and found significant and negative correlation between the two (R: -0.331, *P* < 0.01), indicating that as MELD score increased, the tongue thickness decreased and may be read as worsening of sarcopenia with worsening of liver disease. We also found significant difference in tongue thickness between CTP class C patients and healthy individuals and between CTP class C patients compared to CTP class A and B patients. However, we did not find any significant difference in tongue thickness between healthy individuals and CTP class A and B patients. Apparently, the sarcopenia in appreciable degree manifests only further in the disease course of cirrhosis of liver when patient qualifies for CTP class C categorisation. Similar to our findings, Montano-Loza *et al*[11] studied 248 patients and found that sarcopenia was more prevalent in patients with CTP class C (*P* < 0.05) and in patients with higher MELD scores(*P* < 0.02). In another study, Thandassery *et al*[6] and Tandon *et al*[12] also concluded correlation between prevalence of sarcopenia and disease severity, as measured by L3SMI and CTP.

In this study, we however did not find any correlation between tongue thickness and L3SMI. We also did not find any significant difference in L3SMI of healthy subjects and of Child C patients. Measuring mass of muscles or group of muscles that predominantly have dynamic or postural functions, we believe, is flawed andthe paravertebral muscles being postural muscles, are apparently affected in appreciable degree only late in the disease when patient might be critically ill and gets bed ridden. None of our patients included in this study were critically ill and/or admitted to intensive care unit or were bed ridden, and this could possibly be the reason for us finding no difference between L3SMI of healthy subjects and Child C patients. The reasoning may also be inferred from the study of 116 patients of cirrhosis with hepatocellular carcinoma by Meza-Junco *et al*[13]. In their study, similar to our findings, the degree of sarcopenia measured using L3SMI did not correlate with CTP or MELD scores. However, in our study, the tongue thickness was consistently and significantly decreased in child C patients. Tongue thickness is probably a more sensitive marker of sarcopenia compared to L3SMI and needs further exploration.

Significant number of people of age above 65 years have decreased muscle mass[14]. In this study, we did not include patients above 65 years of age, but for subjects included in this study, we found no significant correlation between tongue thickness and the age of the subjects (Table 4). Sarcopenia in cirrhotic patients has been associated with increased mortality, sepsis, hyper-ammonemia, overt hepatic encephalopathy, and increased length of stay after liver transplantation[6]. Literature also suggests that patients of cirrhosis with poor nutritional status and sarcopenia have a higher risk of mortality, independent of the Child-Pugh and MELD scores[15].It is therefore important to diagnose, quantify and perhaps classify degree of sarcopenia for medical management of patients with cirrhosis of liver, and to be considered while prognosticating outcome of disease and for planning intervention like liver transplant. The exercise could be greatly helped by having a readily available and reproducible method for diagnosis and for quantifying the sarcopenia.

Tongue offers advantage of direct inspection and ease of bedside measurement of thickness using USG, which is more readily available than CT scan and is without the risk of radiation exposure, and unlike CT scan requires no extensive training. Tongue thickness, as suggested by our findings, besides being objective, reproducible and easy, could be a more sensitive index for detecting sarcopenia than L3SMI. Our study was limited on account of being located at a single centre, and directed at patients of only a single disease, namely cirrhosis of liver. Further studies exploring USG-measured tongue thickness in people of diverse ethnicity and different age groups in health and in disease, may be done to explore and validate our finding and to establish this as a convenient bedside tool to diagnose sarcopenia. In view of the findings of our study, authors propose considering tongue thickness measurement using ultrasonography for diagnosis and quantification of sarcopenia.

**ARTICLE HIGHLIGHTS**

***Research background***

Sarcopenia in patients of chronic liver disease has prognostic implications. L3 skeletal muscle index (L3SMI) calculated from computed tomography (CT) scan images is currently the only objective and reproducible method accepted for quantification of sarcopenia. This study aims to explore tongue thickness measured using ultrasonography as an alternative method to document sarcopenia.

***Research motivation***

Sarcopenia in patients of chronic liver disease has prognostic implications. Wider application of L3SMI calculated from CT scan images is however limited by cost, need for extensive training, limited availability and due to risk of radiation exposure. Clinical researchers have been suggesting inclusion of a measure of sarcopenia in established prognostic models for patients of liver disease. A dependable and reproducible method with wider availability is therefore needed.

***Research objectives***

This study aimed to explore tongue thickness measured using ultrasonography as a dependable bedside tool for diagnosis of sarcopenia. Significant differences were seen in tongue thickness between healthy individuals and individuals with less severe liver disease compared to patients with more severe chronic liver disease.

***Research methods***

Patients of chronic liver disease and healthy individuals sequentially satisfying inclusion criteria were studied for tongue thickness using ultrasonography. The study was observational in nature and no intervention was planned on the basis of observations made. Tongue thickness measured was compared between healthy individuals and patients with different severity of liver disease. The imaging technique deployed was ultrasonography, which has wider availability and does not involve risk of radiation exposure unlike CT scan used to measure L3SMI.

***Research results***

Significant differences were seen in tongue thickness between healthy subjects and patients of less severe liver disease compared to patients with more severe liver disease. Tongue thickness measured using ultrasonography is therefore proposed as a bed-side measure of sarcopenia. However, its application needs to be further validated by studies in subjects of different ethnicity, in health and in disease.

***Research conclusions***

This study establishes consistent and significantly reduced tongue thickness in patients with severe liver disease compared to healthy individuals and patients with less severe liver disease. Tongue thickness measured using ultrasonography, authors propose, may therefore be used as a bed side tool for diagnosis of sarcopenia, an application with wide availability and no risk of radiation exposure compare to CT scan-based measure of L3SMI.

***Research perspectives***

Findings of this study needs to be validated by similar study of tongue thickness using ultrasonography in people of different ethnicity in health and in disease.

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**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the Review Board of Institution of liver and Biliary Sciences, New Delhi, India.

**Clinical trial registration statement:** The study titled ‘Study of thickness of tongue by ultrasound and its relation with severity of disease in patients with cirrhosis of liver: Prospective Study, is registered with clinical trials registry of India vide No. CTRI/2017/10/010103.

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

**Conflict-of-interest statement:** No conflict of interest to declare.

**Data sharing statement:** There is no additional data available.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

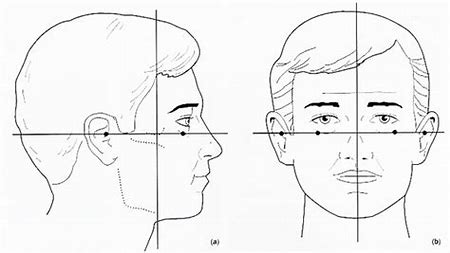
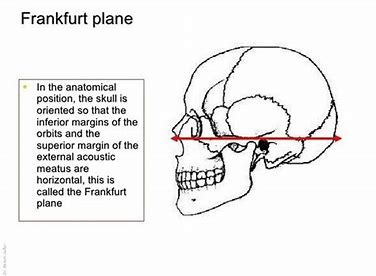
Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Imazeki F, Sabouri AS **S-Editor:** Wang J **L-Editor:** **E-Editor:**

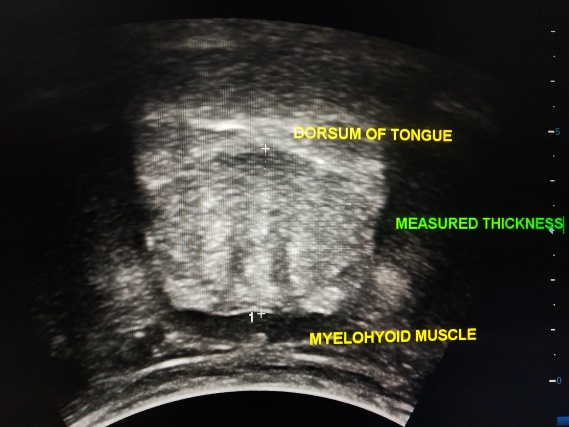
**Figure Legends**



Probe directed at right angle to Frankfurt Plane

Frankfurt horizontal line

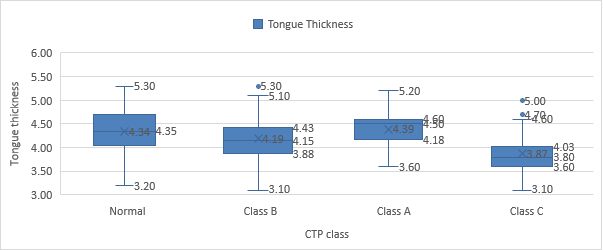
**Figure 1 Ultrasonography probe position for measuring tongue thickness.**



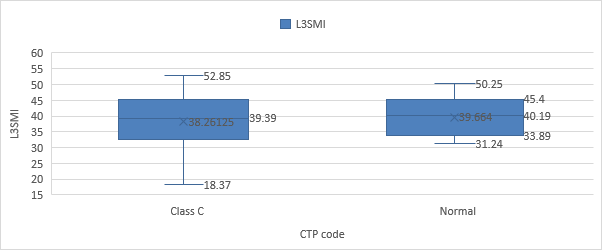
USG probe

**Figure 2 Vertical distance measured from the surface of mylohyoid muscle to the tongue dorsum.** USG: Ultrasonography.

**Figure 3 Aetiologies for cirrhosis of liver.**



**Figure 4 The Boxplot of distribution of tongue thickness in different “Child Turcotte Pugh” class and normal healthy subjects.** CTP class: Child Turcotte Pugh class.



**Figure 5 Box Plot of distribution of L3 skeletal muscle index in Child Turcotte Pugh class C and healthy individuals.** L3SMI: L3 skeletal muscle index; CTP class: Child Turcotte Pugh class.

**Table 1 Tongue thickness in study groups**

|  |  |  |
| --- | --- | --- |
| **Study group** | **Mean ± standard deviation** | **Median (range)** |
| Child class A | 4.39 ± 0.39 cm | 4.50 cm (Range 4.25-4.53) |
| Child class B | 4.19 ± 0.53 cm | 4.15 cm (Range 3.99-4.39) |
| Child class C | 3.87 ± 0.42 cm | 3.80 cm (Range 3.71-4.02) |
| Normal (healthy) subjects | 4.33 ± 0.49 cm | 4.35 cm (Range 4.15-4.51) |

**Table 2 Comparison of tongue thickness in study groups**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **(I) CTP class** | **(J) CTP class** | **Mean difference (I-J)** | **Std. error** | **Significance** | **95% Confidence interval** | |
| **Lower bound** | **Upper bound** |
| Class A | Class B | 0.2000 | 0.1186 | 0.335 | −0.109 | 0.509 |
| Class C | 0.5233a | 0.1186 | 0 .000 | 0.214 | 0.832 |
| Normal | 0.0567 | 0.1186 | 0.964 | −0.252 | 0.366 |
| Class B | Class A | −0.2000 | 0.1186 | 0.335 | −0.509 | 0.109 |
| Class C | 0.3233a | 0.1186 | 0.037 | 0.014 | 0.632 |
| Normal | −0.1433 | 0.1186 | 0.623 | −0.452 | 0.166 |
| Class C | Class A | −0.5233a | 0.1186 | 0.000 | −0.832 | -0.214 |
| Class B | −0.3233a | 0.1186 | 0.037 | −0.632 | -0.014 |
| Normal | −0.4667a | 0.1186 | 0.001 | −0.776 | -0.158 |
| Normal | Class A | −0.0567 | 0.1186 | 0.964 | −0.366 | 0.252 |
| Class B | 0.1433 | 0.1186 | 0.623 | −0.166 | 0.452 |
| Class C | 0.4667a | 0.1186 | 0.001 | 0.158 | 0.776 |

aStatistically significant. CTP class: Child Turcotte Pugh class.

**Table 3 Correlation between “Model for end stage liver disease” score and tongue thickness**

|  |  |  |  |
| --- | --- | --- | --- |
|  | | **Tongue thickness** | **MELD score** |
| Tongue thickness | Pearson correlation | 1 | −0.330a |
| Significance (2-tailed) |  | 0.001 |
| N | 120 | 90 |
| MELD score | Pearson correlation | -0.330a | 1 |
| Significance (2-tailed) | 0.001 |  |
| N | 90 | 90 |

aStatistically significant. MELD score: Model for end stage liver disease score.

**Table 4 Correlation between age and tongue thickness**

|  |  |  |  |
| --- | --- | --- | --- |
|  | | **Tongue thickness** | **Age** |
| Tongue thickness | Pearson correlation | 1 | −0.081 |
| Significance (2-tailed) |  | 0.382 |
| N | 120 | 120 |
| Age | Pearson correlation | −0.081 | 1 |
| Significance (2-tailed) | 0.382 |  |
| N | 120 | 120 |

**Table 5 Correlation between tongue thickness and L3 skeletal muscle index**

|  |  |  |  |
| --- | --- | --- | --- |
|  | | Tongue thickness | L3SMI |
| Tongue thickness | Pearson correlation | 1 | -0.074 |
| Significance (2-tailed) |  | 0.424 |
| N | 120 | 120 |
| L3SMI | Pearson Correlation | -0.074 | 1 |
| Significance (2-tailed) | 0.424 |  |
| N | 120 | 120 |

L3SMI: L3 skeletal muscle index.

**Table 6 Comparison of L3 skeletal muscle index in Child Turcotte Pugh class C and normal healthy subjects**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **CTP class** | **L3SMI** | | | | | ***P* value** |
| **Mean** | **Standard deviation** | **Median** | **Minimum** | **Maximum** |
| Class C | 38.2613 | 8.88428 | 39.3900 | 18.37 | 52.85 | 0.63 |
| Normal | 39.6640 | 6.80565 | 40.1900 | 31.24 | 50.25 |  |

L3SMI: L3 skeletal muscle index; CTP class: Child Turcotte Pugh class.

**Table 7 Intraclass correlation coefficient for ultrasonography measures of tongue thickness**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Intraclass correlation** | **95% Confidence interval** | | ***F* test with true value 0** | | | |
| **Lower bound** | **Upper bound** | **Value** | **df1** | **df2** | **Sig** |
| Single measures | 0.954a | 0.939 | 0.966 | 63.487 | 119 | 238 | 0.000 |
| Average measures | 0.984a | 0.979 | 0.989 | 63.487 | 119 | 238 | 0.000 |

aStatistically significant. Sig: Significance.