



Liver, Pancreas and Biliary Tract

Muscle psoas indices measured by ultrasound in cirrhosis – Preliminary evaluation of sarcopenia assessment and prediction of liver decompensation and mortality

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ABSTRACT

Background: No data on the European population exists regarding the use of an ultrasoundbased measurement of psoas diameter for sarcopenia assessment in cirrhosis.

Aims: To determine the applicability of an ultrasound measurement of the psoas muscle diameter in patients with decompensated liver cirrhosis and to assess whether this surrogate is associated with hospitalization due to decompensation and mortality.

Methods: In 75 consecutive patients with decompensated liver cirrhosis and in 20 control subjects (January 2016 to November 2017), psoas muscle diameter was prospectively measured. The reliable measurements were used for the further analysis. Relevant clinical and laboratory data was collected.

Results: Ultrasound measurement was applicable in 100% of control and in 72% of study subjects. Psoas to height ratio was significantly related to hospitalization and mortality ($p < 0.0001$, HR 0.717, 95% CI: 0.622–0.828 and $p = 0.022$; HR = 0.825, 95% CI: 0.701–0.973) as was psoas muscle index ($p < 0.0001$, HR = 0.881, 95% CI: 0.836–0.929 and $p = 0.017$; HR = 0.930, 95% CI: 0.876–0.987).

Conclusions: Ultrasound measurement of psoas muscle diameter and its derived indices is applicable and associated with hospitalization and mortality in patients with decompensated liver cirrhosis.

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1. Introduction

Liver cirrhosis is the final stage in the course of liver fibrosis progression, which accompanies many chronic liver diseases. It is clinically presented in a compensated or decompensated phase, the latter characterized by the appearance of ascites, variceal haemorrhage, infections, hepatic encephalopathy, hepatorenal syndrome or jaundice [1]. Malnutrition often complicates cirrhosis [1–3]. It is found in about 20% of patients in the compensated stage (stage 1 and 2), while in the decompensated stage of disease (stage 3–5), this percentage extends up to over 60% [2]. Due to severe prognostic implications of malnutrition, nutritional status should be always assessed in patients with cirrhosis, in particular in the decompensated stage of the disease [4]. In 2018, the European Association for

the Study of the Liver (EASL) issued guidelines regarding nutrition of patients with chronic liver disease [4], underlining that simple non-invasive tests for a better risk stratification of malnutrition and its complications are needed.

Sarcopenia is the most evident consequence of malnutrition. It is defined as a loss of muscle mass and decreased muscle strength and function. The loss is not solely due to muscular atrophy, but also involves the replacement of muscle with fat (myosteatosis) and connective tissue [1,2,5,6].

In cirrhosis, sarcopenia has been implied in the pathophysiology of decompensation, and it is associated with a higher risk of death [7–9]. For this reason, the early recognition of sarcopenia in a patient with liver cirrhosis is important. It points out patients with higher risk of decompensation and death, requiring interventions aimed at improving muscle mass, and consequently potentially improving survival. In daily practice, anthropometric measurements (BMI, triceps skin fold – TSF, mid arm circumference – MAC), hand-grip test and more demanding measurements

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of muscle and fat mass (DEXA – dual-energy X ray absorptiometry; BIA – bioimpedance analysis) have been proposed [4].

In recent years, clinical research has focused on finding direct indicators of skeletal muscular mass volume in cirrhosis [10]. Measurements on cross-sectional imaging (mostly CT scan) of the diameter and area of the psoas muscle and erect spinae muscle, or its derived indices – PMI (Psoas muscle index), PMTH (Psoas muscle to height ratio), PMA (Psoas muscle area) and SMI (Skeletal muscle index) have been proposed [11–13]. However, CT scan is not always readily available, is not a point-of-care test and is associated with not negligible cost and irradiation [13]. In addition, cut-off values of these indices are only partially validated in patients with cirrhosis [4,14,15]. Tandon et al. proposed a model for the evaluation of sarcopenia by means of ultrasonic measurement of the thigh muscle diameter which is moderately accurate in comparison to psoas CT/MR measurement, but has not been validated against clinical endpoints [11].

A method to measure the diameter and cross section of the psoas muscle on ultrasound has been described by two Japanese studies in healthy subjects and in patients with cirrhosis showing a good correlation with CT-based measurements of the psoas [16,17], but no data about the applicability of ultrasound for the study of psoas muscle in the European population is available. Furthermore, US-based measurements of psoas have not been studied as a predictor of hard clinical endpoints in patients with decompensated cirrhosis.

Given the above mentioned considerations, and given that ultrasound is safe, simple and not expensive, the primary goal of our study was to determine the applicability of an ultrasound measurement of the psoas muscle diameter in patients with decompensated liver cirrhosis.

The secondary objective was to assess whether this surrogate of sarcopenia correlates with clinical outcomes (hospitalization due to further decompensation, and mortality) in this population.

2. Materials and methods

We obtained the approval of the Medical Ethics Committee of the Republic of Slovenia for a retrospective analysis of the prospectively collected data (No. 0120-448/2018/9). Informed consent was obtained from each patient included in the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a prior approval by the institution's human research committee.

2.1. Study population

For the purposes of the observational study, an ultrasound examination was carried out between January 2016 and November 2017. Based on previous studies regarding ultrasound assessment of muscle mass [18–20], and considering (a) that the inclusion of decompensated patients would result in a high proportion of liver-related events and (b) based on a preliminary analysis of the results at the inclusion of 50 cases as for the reliability of the measurement, the final sample size was set at 75 cases.

We included patients with a history of decompensation or currently decompensated liver cirrhosis. Patients were selected among those requiring an ultrasound examination for regular HCC surveillance at Department of Gastroenterology of the General Hospital Celje. Inclusion factors were: presence of cirrhosis according to clinical and radiological criteria (US or CT morphological signs of liver cirrhosis, elastographic signs of liver cirrhosis, laboratory signs of impaired liver function according to the CHILD score) [21]; presence of ongoing or previous decompensation defined as ascites, varicose bleeding, hepatic encephalopathy, jaundice or severe bacterial infection (requiring hospital treatment) within one

year before being included in the study. The presence of ascites was confirmed in all cases by ultrasound. Ascites should have been a transudate (SAAG > 11 g/L). The existence of hepatic encephalopathy or jaundice was defined according to the EASL guidelines [22,23]. Extrahepatic cause of jaundice was excluded with US in all cases. Varicose haemorrhage was confirmed by gastroscopy. Signs of infection requiring hospitalization were defined as an acute increase of inflammatory blood indicators (CRP, procalcitonin) and the need for antibiotic treatment. We did not include patients with known HCC or any other active cancer, otherwise there was no exclusion criteria.

A control group 20 subjects was studied in the same time period in parallel from the cohort with no chronic disease of the internal organs and with no known active cancer. Patients were selected among those requiring an ultrasound examination at Department of Gastroenterology of the General Hospital Celje. If they agreed to participate in the study, they were not to have a known chronic liver disease, nor should they show ultrasound evidence of advanced liver fibrosis or signs of clinically significant hepatic steatosis (assessed as hyperechoic liver parenchyma in relation to the renal parenchyma).

Sex, age, height and weight, as well as data on the etiology of liver disease and previous or ongoing decompensation were collected using the electronic case record system of our center. In addition, standard laboratory data on liver and kidney function were recorded. In the control group, we collected the following clinical data: sex, age, height, weight and BMI.

2.2. Muscle psoas measurement

An ultrasound examination was performed by a hepatologist with the knowledge that exceeded the necessary learning curve (more than 5000 examinations). The investigator was not aware of laboratory characteristics. The subject was in fasting condition for at least 6 h and was lying on the back during the examination. All measurement were done using the Esaote MyLab Eight™ (Genoa, Italy) device using a monocrystalline high frequency abdominal probe. The investigation was carried out in the ultrasound department of the Department of Gastroenterology, General Hospital Celje.

Right psoas muscle and concomitantly lying lumbar vertebrae were accurately recognized in each patient. Abdominal probe was positioned in a sagittal plane subphrenally right and just above the upper anatomical limit of the pelvis (iliac crest). Sliding the ultrasonic probe in the anteromedial to posterolateral direction, the largest ultrasonically visible psoas muscle diameter was defined (Figs. 1 and 2). The measurement of the muscle diameter in millimeters (mm) was done in triplicate. The average of the three measurements was used as a final result in mm rounded to the nearest tenth of the unit. We defined as “reliable” the psoas muscle measurements fulfilling all the following criteria: (a) all the mentioned anatomical boundaries could be clearly identified; (b) maximum psoas diameter between each of the three measurements did not deviate from the remaining two by more than 5 mm.

Measurements that did not meet these criteria were considered unreliable and were not included in the final analysis. Factors associated with unreliable results were specifically assessed.

In analogy to what is proposed for CT-based psoas-derived indices, we calculated the Ultrasound Psoas to height ratio (US-PTHR) as mean of psoas diameter divided by patient's height (unit in mm/m) and the Ultrasound Psoas muscle index (US-PMI) as Π *psoas radius square divided by patient's height square (unit in cm^2/m^2).

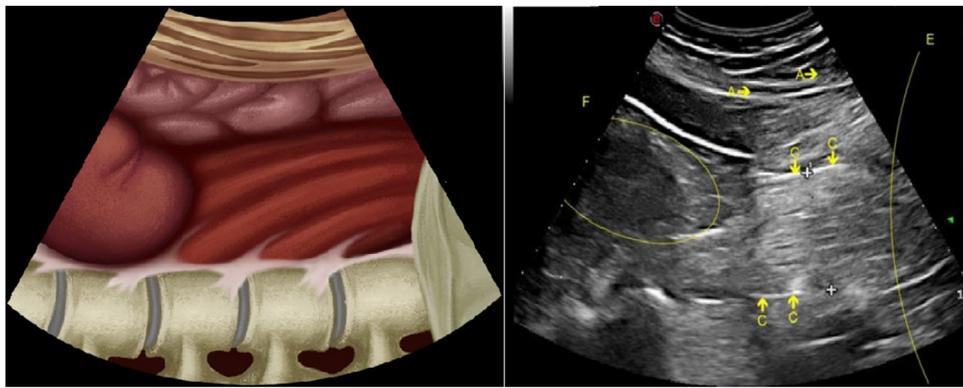


Fig. 1. Left side: anatomic scheme of the ultrasound picture with important organs and parts drawn. Right side: ultrasound measurement of the psoas muscle diameter in a healthy individual. A – subcutaneous fatty tissue, C – psoas muscle edges, E – the approximate position of the iliac crest, F – inferior pole of the right kidney.



Fig. 2. Ultrasound measurement of the psoas muscle diameter in a patient with liver cirrhosis. Left side: A – subcutaneous fatty tissue, B – intestinal structures, C – psoas muscle edges, D – anterior edge of the lumbar vertebrae, E – the approximate position of the iliac crest, F – inferior pole of the right kidney. Right side: Measurement of the largest visible psoas muscle diameter. A – psoas muscle edges.

2.3. Statistical analysis

US-PTHR was rounded to the closer entire unit of measurement, and US-PMI was rounded to the closer unit with one decimal. Demographic and clinical data of the population including laboratory data and ultrasound measurements were put in an electronic database (SPSS Inc., Chicago, IL USA) for statistical analysis. Descriptive summary statistics of the population were performed. Summary values were described as the average \pm standard deviation (SD) and/or as a median, range and interquartile range when appropriate (according to the distribution of the processed data). Comparisons between patients and healthy controls were done using T-test and Chi square as appropriate. Univariate and multivariate analyses were performed using Cox model and logistic regression. In order to evaluate the correlation between numerical variables, a multi-linear regression analysis was performed. The statistical analysis was carried out with the SPSS 22.0 package (SPSS Inc., Chicago, IL USA). The alpha value was set at 0.05. All p-values were two-sided.

3. Results

The main clinical characteristics of patients in the study and the control group are given in Tables 1 and 2.

3.1. Applicability of ultrasound for psoas muscle measurement in patients with decompensated cirrhosis

Ultrasound measurement of the psoas muscle diameter was successful and reliable in 54 (72%) out of 75 included patients. In the remaining 21 patients the measurement was possible of poor qual-

Table 1

Main clinical characteristics of the included patients.

| Variable | Study group (n = 54) | Control group (n = 20) |
|--|----------------------------|---------------------------|
| Age, yrs | 63 \pm 11 | 57 \pm 15 |
| Males, n (%) | 39 (72%) | 14 (70%) |
| BMI, kg/m ² (range) | 28.1 \pm 5.3 | 27.8 \pm 3.5 |
| BMI obese, n (%) | 16 (32%) | |
| Cirrhosis etiology (alcohol/NAFL-NASH/other), n (%) | 36/8/10 (67/15/18%) | |
| Ascites, n (%) | 42 (78%) | |
| Encephalopathy, n (%) | 15 (28%) | |
| Varices, n (%) | 35 (71%) | |
| Creatinine (μ mol/L) | 86 \pm 32 | |
| Bilirubin (μ mol/L) | 64 \pm 112 | |
| AST (μ U/L) | 1.1 \pm 0.8 | |
| ALT (μ U/L) | 0.8 \pm 0.6 | |
| Albumin (g/L) | 34 \pm 8 | |
| INR | 1.4 \pm 0.3 | |
| Platelet count (n [*] 10 ⁹ /mm ³) | 131 \pm 71 | |
| Na-MELD score | 15 \pm 7 | |
| CHILD score | 8 \pm 2 | |
| Developed HCC in the follow up, n (%) | 7 (13%) | |
| Cause of hospitalization in the follow-up (infection/ascites/HE/other), n (%) | 9/14/8/5 (25/39/22/14%) | |
| Cause of death (infection/HCC/other), n (%) | 5/6/4 (33/40/27%) | |

ity (unreliable) in 7 (9,3%) and in 14 (18.7%), the measurement was not possible at all. The acquisition of any measurement was thus estimated to be possible in approximately 80% of the study population. Measurement was less reliable in patients with very high

Table 2

Psoas diameter, US-PTHR and US-PMI data of the included patients. The p value refers to the comparison of patients with cirrhosis and controls.

| Variable | Patients with cirrhosis (n=54) | Control group (n=20) | p |
|--|--------------------------------|----------------------|------------|
| Psoas diameter (mm) | | | p < 0.0001 |
| Median | 34 | 41 | |
| Min–Max | 20–46 | 32–48 | |
| IQR | 5 | 7 | |
| US-PTHR (mm/m) | | | p < 0.0001 |
| Median | 20 | 24 | |
| Min–Max | 13–26 | 20–28 | |
| IQR | 3 | 2 | |
| US-PMI (mm ² /cm ²) | | | p < 0.0001 |
| Median | 3.2 | 4.5 | |
| Min–Max | 1.2–5.5 | 3.1–6.0 | |
| IQR | 0.9 | 0.8 | |

or very low abdominal circumference. As expected, interposition of abdominal gas from the surrounding structures was observed. In addition, the measurement was slightly influenced by the investigator's experience, since an increase in frequency of successfully obtained measurements was reported at the later stage of the study. Other contributing factors affecting the measurement were the presence of ascites and the general state of the patient (difficulties to lay still on the back).

In reliable measurements, the average psoas diameter was 34 mm (range: 20–46; SD 5; IQR 5 mm). The estimated relative error of ultrasonic measurement was 0.08 (8%) (absolute measurement error 3 mm). As expected, the obtained values varied largely among subjects, and therefore, the values were indexed to patients' height (US-PTHR and US-PMI) for further analysis (Table 2). The average US-PTHR value was 20 mm/m (range: 13–26; IQR 3 mm/m) and the average US-PMI was 3.2 cm²/m² (range: 1.2–5.5, IQR 1.0 cm²/m²).

3.2. Applicability of ultrasound for psoas muscle measurement in control subjects

In the control group, the ultrasound measurement of the psoas muscle diameter was successful and reliable in 20 out of 20 included subjects (100%).

The average psoas diameter was 41 mm (range: 32–48; IQR 7 mm). The average US-PTHR value was 24 mm/m (range: 20–28; IQR 2 mm/m). The average US-PMI was 4.5 cm²/m² (range: 3.2–6.0; IQR 0.8 cm²/m²).

US-PTHR and US-PMI were significantly higher in control subjects vs. patients (p < 0.0001 in both cases, confirmed after adjustment for age and gender).

3.3. Ultrasound-based Psoas muscle indices and hospitalization due to further decompensation in cirrhosis

The median follow-up was 12 months. Over the follow-up 37 patients (68.5%) needed hospitalization due to further decompensation of cirrhosis (9 due to infection, 14 due to the clinically relevant ascites and 8 due to the hepatic encephalopathy; in some instances these were associated with variceal haemorrhage, alcoholic hepatitis and acute kidney injury).

Both US-PTHR and US-PMI were associated with risk of hospitalization due to further decompensation of cirrhosis with an odds ratio of 0.16; (95% CI 0.05–0.50; p = 0.002) and 0.58 (95% CI 0.42–0.81; p = 0.002), respectively. The result confirms that a higher muscle mass, assessed by ultrasound is associated with lower hospitalization due to the further occurrence of any type of liver cirrhosis decompensation. After adjusting for gender, the results did not change.

Fig. 3 shows the probability of hospitalization due to further decompensation of cirrhosis according to an US-PTHR above or

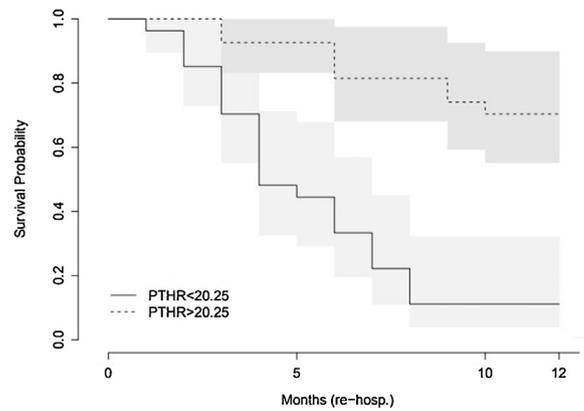


Fig. 3. Probability of hospitalization due to further decompensation of cirrhosis according to US-PTHR above or below the median in the study population. The grey areas indicate the 95% CI. PTHR – psoas to height ratio.

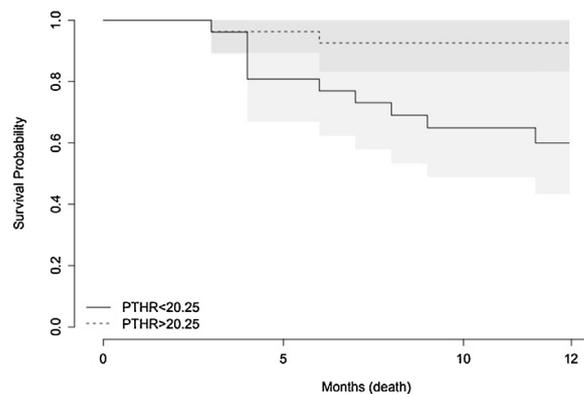


Fig. 4. Probability of survival according to US-PTHR above or below the median in the study population. The grey areas indicate the 95% CI. PTHR – psoas to height ratio.

below the median in the present series. As shown, the actuarial risk of hospitalization at 12-months was about 65% in patients with US-PTHR below the median, while it was only 10% in patients with US-PTHR above the median. On multivariate analysis adjusted for MELD, CHILD and presence of varices, either US-PTHR (HR 0.717; 95% CI: 0.622–0.828; p < 0.0001) or US-PMI (HR = 0.881, 95% CI: 0.836–0.929; p < 0.0001) remained independently associated with hospitalization due to further decompensation of cirrhosis.

3.4. Ultrasound-based Psoas muscle indices and mortality in cirrhosis

Over the follow-up, 15 patients died (27.8%). Median survival time was 8.0 months (95% CI: 5.3–10.7) and restricted mean survival time was 11.7 months (95% CI: 9.3–14.0).

The cause of death was liver-related in 12 (bacterial infection in 5; HCC in 6; variceal bleeding in 1); 2 patients died for sudden cardiac arrest; in one case the cause of the death could not be established. On multivariate analysis adjusted for MELD score US-PTHR was related to mortality (p = 0.022; HR = 0.825, 95% CI: 0.701–0.973), as was US-PMI (p = 0.017; HR = 0.930, 95% CI: 0.876–0.987) being the likelihood of mortality lower as US-PTHR (or US-PMI) increase (Fig. 4).

4. Discussion

The main finding of this retrospective analysis of prospectively collected data at a single secondary hospital center is that ultra-

sound measurement of the psoas muscle diameter and derived indices in patients with decompensated cirrhosis is applicable and shows clinical relevance, since it correlates with the further decompensation requiring hospitalization and risk of death in this population. Looking closer at the technical aspects, our study indicates about 80% success of the acquisition of any measurement and 72% success of obtaining a reliable measurement. These figures were lower as compared to applicability in the control group devoid of cirrhosis, which was 100%. While our results in healthy subjects are consistent to those of a previous report from Japan [16], the applicability in our patients with cirrhosis is significantly lower to that reported by Kobajashi et al. (100% applicability of the cross section psoas measurement at the right groin area) [17]. Differences in the imaging protocol (scanning site: right subphrenal position in our study vs. right groin area in the study from Japan [17] and in the body habits between the asiatic and caucasian population might partly explain this difference. However, we have chosen to measure the muscle diameter in a right subphrenal position since in our previous pilot experiences the visualization of the psoas at the groin area is often blurred in decompensated cirrhosis due to ascites or intestines air interposition. Nonetheless, also using our scanning protocol very high or very low waist circumference were associated with a limited applicability. In this sense, the CT obtained measurement of the psoas muscle diameter has an important advantage, since it is a statically captured image, which is then easily measured by a doctor who has no experience in performing this investigation [4,13], and can be done irrespective of waist circumference or decompensated state of disease. Also, due to the position of the maximal diameter of the psoas muscle (the direction of the diameter is posterolateral - anteromedial in sagittal plane), the largest diameter can be more accurately measured by CT investigation. Additionally, the psoas derived parameters alone may not be as accurate as when considering all the muscle area at specific lumbar level, which according to accepted guidelines should represent the golden standard to assess sarcopenia [4].

On the other hand, we observed in our study that, in the case of clearly identifiable anatomical boundaries and in the hands of an experienced investigator, the determination of the maximum muscle diameter had a low variability. Ascites worsened the visualization of the psoas muscle by ultrasound, and this might constitute an important obstacle to the introduction of the proposed ultrasound method into everyday practice. As a possible solution, the ultrasound measurement could be done directly after the puncture of ascites. A clear limitation of our study is the lack of comparison with CT measured psoas muscle diameter, which would require a specifically designed study.

Even if the above mentioned limitations exist, in our population of decompensated patients, we have demonstrated that ultrasound based PTHR and PMI are associated with risk of further decompensation leading to hospitalization. Contrarily to previous studies on sarcopenia assessed on CT scan, we were unable to show sex differences in this context [4,13,15,24]. This is probably due to the low prevalence of women in our population, which is expected due to the epidemiology of liver disease in Slovenia (mostly due to alcohol abuse, which is far more common in men). We also failed to prove that sarcopenia is a risk factor for early rehospitalization (<3 months), which is reported in several studies on sarcopenia in liver transplantation candidates [24,25]. We believe that in the population of patients awaiting liver transplantation, the rate of sarcopenia might be higher than in our patient group, which might affect the higher chance for very early decompensation (within 3 months) and mortality.

The next result of our study is that the ultrasound-based indices of psoas diameter independently predict mortality in patients with decompensated liver cirrhosis. Similar investigations have used CT to evaluate sarcopenia, with similar conclusions [26–30] According

to Montano-Loza, the rate of sarcopenia should be an important indicator for clinical decision-making, and liver transplantation would bring an important benefit in a group with severe rate of sarcopenia [31,32]. Ultrasound-based methods have the big advantage of providing a simple and point-of-care assessment, potentially simplifying risk stratification and decision making in decompensated patients. Although our study did not define the limit values of ultrasound-based sarcopenia indices, it could be the basis for an additional study defining these values.

We acknowledge that our study has limitations that should be taken into account on interpreting its results. First, it is a retrospective and monocentric data analysis, including a small number of patients. Also, ultrasound investigation was carried out by only one investigator and we cannot provide data on inter-observer reproducibility. We are aware that our investigation does not provide comparison with CT scan images, which are currently considered the best available standard, and did not assess other muscle-related factors that have a significant effect on outcomes in patients with liver cirrhosis (e.g. the impact of muscle function and the effect of fat and connective tissue transformation of skeletal muscles). In addition, according to some authors, in females adipopenia (loss of subcutaneous and visceral fat) could play an important prognostic role, and the reported ultrasound-based method does not allow assessing this aspect [33]. Another possible limitation of the method we are proposing depends on the reduced reliability in patients with very high abdominal circumference. This might imply that in NASH patients, which are most of the time obese, this method might not be sufficiently exact to study sarcopenia. Studies focusing on this specific population are therefore needed.

Despite these limitations, the results of this study underline the feasibility and good applicability of a simple, readily available and point-of care ultrasound method to measure psoas muscle diameter as a surrogate of sarcopenia in decompensated patients with cirrhosis. US-based psoas measurement held prognostic value for further decompensation and mortality in our population. In our view, the routine use of this method during ultrasound examination of patients with decompensated cirrhosis should be attempted to enable early identification and monitoring of sarcopenia in this group of patients.

Conflict of interest

None declared.

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