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Ultrasound muscle assessment for sarcopenia detection in inflammatory bowel disease: A prospective study

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Abstract

Background: Sarcopenia is prevalent in patients with inflammatory bowel disease (IBD) and impacts surgical and therapeutic outcomes; thus, effective diagnostic tools are needed to assess muscle mass and function in this population.

Methods: 153 consecutive patients were included, 100 in the *training cohort* and 53 in the *study cohort*. Three superficial muscles (rectus femoris = RF, rectus abdominis = RA, and biceps brachii = BB) were selected for the detection of sarcopenia using muscle ultrasound (US). The *training cohort* consisted of consecutive patients with or without IBD and was used to evaluate the feasibility and inter- and intra-observer variability of the US measurement. The *study cohort* consisted of only IBD patients and served to test US diagnostic accuracy. In the *latter*, muscle US, bioelectrical impedance analysis (BIA), and magnetic resonance imaging (MRI) were used to measure muscle parameters.

Results: Sarcopenia prevalence in IBD patients was 50%. Muscle US showed excellent inter-rater and intra-rater reliability (ICC >0.95) and a good diagnostic accuracy in detecting sarcopenia compared to BIA with area under the receiver operating characteristic curve (AUROC) values of 80% and 85% for RA and BB thickness, respectively. Moreover, an Ultrasound Muscle Index (USMI) was defined as the sum of the RA, BB, and RF thickness divided by the square of the patient's height, resulting in an AUROC of 81%. Muscle thresholds for sarcopenia were detected, with RA and USMI values correlated with the highest positive (84.3%) and negative (99%) predictive values, respectively. Additionally, the agreement between the US and MRI measurements of RA was excellent (ICC 0.96).

Conclusions: The findings of this study emphasize the potential of muscle US as a reliable diagnostic tool for assessing sarcopenia in IBD patients. This research has significant implications for disease management in IBD patients and underscores the need for further investigations to validate these findings in larger cohorts.

KEYWORDS
bioelectrical impedance analysis, Crohn's disease, diagnostic tools, disease activity, magnetic resonance imaging, malnutrition, ulcerative colitis, ultrasound muscle index, USMI

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition with challenges extending beyond intestinal symptoms. Among these, skeletal muscle health is emerging as a pressing concern, as sarcopenia is associated with poor clinical outcomes, including higher rates and prolonged hospitalization, increased postoperative complications, and treatment failure.[1–3]

Sarcopenia, defined as loss of muscle mass, strength, and function,[4] was initially considered to be exclusively a disease of the elderly (primary sarcopenia). However, emerging evidence points to early sarcopenia (secondary sarcopenia) in patients with chronic diseases.[5] Sarcopenia has been reported in IBD patients, affecting 12% of individuals with a mean age of 31 years,[6] and reaching up to 52% in specific cohorts of patients with Crohn's Disease (CD).[7]

Possible mechanisms of sarcopenia in IBD include chronic inflammation, protein malabsorption, reduced intake, corticosteroid use, and decreased physical activity.[8] Notably, malnutrition is a recognized risk factor for sarcopenia, but it's noteworthy that a considerable proportion of sarcopenic patients in IBD are overweight or obese.[9]

Current ESPEN guidelines on clinical nutrition in IBD recommend screening for malnutrition and sarcopenia at diagnosis and regularly during follow-up.[10] However, gold standard diagnostic tools like Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans face significant limitations in clinical practice, including limited availability, high cost, time-consuming requirements, lack of portability and the need for specialist staff.[4]

To overcome these limitations, widely accessible tools such as Dual-Energy X-ray Absorptiometry (DXA) and Bioelectrical Impedance Analysis (BIA) have been employed as reference methods for diagnosing sarcopenia in clinical practice. However, established cut-off values for IBD patients are lacking, and scientific knowledge about their utility in this context is limited.[11–14] Additionally, both DXA and BIA fail to assess muscle quality.

Ultrasound (US) has emerged as a promising solution for the screening and diagnosis of sarcopenia in IBD as it is non-invasive, bedside, inexpensive and readily available in clinical practice. US can provide accurate quantitative and qualitative information on muscle function.[15]

Recently, Perkisas et al. defined standardized US measurement approaches, anatomical landmarks, and measurement points for different muscles and muscle groups, paving the way for novel studies.[15] The US method has been shown to be more accurate than cross-sectional imaging and DXA in estimating muscle mass,[16–18] and US assessment of specific muscle parameters and derived indices has shown potential for predicting risk of hospitalization and mortality.[19]

Key summary

Summarise the established knowledge on this subject

- Sarcopenia, characterized by muscle loss and dysfunction, is a common concern in inflammatory bowel disease (IBD) and can occur at a young age.
- Sarcopenia negatively impacts several IBD-related clinical outcomes.
- Current gold standard tools for sarcopenia detection in IBD involve techniques like bioelectrical impedance analysis (BIA) and magnetic resonance imaging (MRI), which can be costly and time-consuming, thus being poorly used in gastroenterology clinical practice. Self-reported questionnaires such as SARC-F and functional tests such as the chair stand test (CST) are often used but may not be as accurate in diagnosing sarcopenia, especially in younger populations such as those with IBD.
- Ultrasound (US) is an emerging and promising tool for assessing muscle parameters and diagnosing sarcopenia.

What are the significant and/or new findings of this study?

- This study revealed a high prevalence of sarcopenia (50%) among IBD patients, emphasizing the importance of early assessment and intervention for this condition in this population.
- Ultrasound (US) measurements of specific muscles (biceps brachii, rectus abdominis, rectus femoris) demonstrated good diagnostic accuracy (AUROC values of 80%–85%) for detecting sarcopenia compared to BIA, which is used as the gold standard.
- The agreement between US and MRI measurements indicated that US can be a reliable and cost-effective alternative to MRI for assessing muscle parameters in IBD patients.
- Sarcopenia can occur in the absence of malnutrition, whereas the study found a moderate negative correlation between US measurements (particularly rectus abdominis thickness and US Muscle Index) and disease activity in IBD patients, suggesting that as disease activity increases, muscle parameters tend to decrease.

To date, no studies have investigated the role of US in the assessment of sarcopenia in IBD patients, and the optimal muscle and parameters have not yet been established. The possibility of rapidly

screening IBD patients using US is an attractive solution to raise awareness of sarcopenia and facilitate timely nutritional interventions.

MATERIALS AND METHODS

Study design, inclusion, and exclusion criteria

This prospective cohort study aimed to assess the feasibility and diagnostic accuracy of US for detecting sarcopenia in patients with IBD. The study was conducted at the Gastroenterology Unit, Fondazione IRCCS San Gerardo dei Tintori Hospital in Monza between February and August 2023.

The primary aim of this prospective study was to assess the diagnostic accuracy of US in evaluating sarcopenia in patients with IBD. Secondary Aims were: (i) Assessment of inter- and intra-observer variability in US measurements; (ii) Comparison of US with MRI muscle measurements; (iii) Evaluation of the relationship between sarcopenia and IBD disease activity indices.

The study consisted of two distinct cohorts: a training cohort and a study cohort (Figure 1: Flowchart of the study).

The *training cohort* included consecutive adult patients with or without IBD referred to our department for various clinical reasons, including but not limited to IBD disease activity control. This cohort was primarily included to assess the feasibility and reliability of US measurements, contribute to the methodological development, standardization of measurements, assessment of inter- and intra-observer agreement, and test potential limitations in the context of IBD patients.

The *study cohort* comprised adult patients with a histologically confirmed diagnosis of IBD and undergoing intestinal US mainly for routinary controls and served to test the accuracy of US in detecting sarcopenia.

All patients in the *study cohort* underwent US muscle measurement and BIA on the same day. Specifically, patients underwent BIA assessment first, followed by the US examination. BIA was used as the reference standard due to its accuracy in sarcopenia diagnosis, associated with lower costs, higher availability, and absence of ionizing radiation exposure as compared to cross-sectional imaging modalities such as MRI or CT scans. Moreover, on the same day participants completed the sarcopenia screening questionnaire (SARC-F) and the chair stand test (CST) to assess muscle strength.[4] Available MRI data were re-evaluated by experienced radiologists. Demographic and clinical data, past and/or current history and treatment of all patients were recorded. Disease activity was assessed using the partial MAYO (pMAYO) score for UC and the Harvey Bradshaw Index (HBI) for CD, and it was categorized into disease remission (pMAYO <2, HBI <5), mild activity (pMAYO 2–4, HBI 5–7), moderate activity (pMAYO 5-7, HBI 8–16), and severe activity (pMAYO >7, HBI>16). Biochemical parameters were recorded if collected within 30 days of the US examination, including complete blood count (CBC), C-reactive protein (CRP), calprotectin, iron, ferritin, albumin, pre-albumin, vitamin D, folate, and vitamin B12.

All patients underwent nutritional status screening using the Malnutrition Universal Screening Tool (MUST) to identify individuals at risk of malnutrition.[20]

For both cohorts, exclusion criteria were: (i) Patients with contraindications for ultrasound examinations; (ii) Patients with severe cognitive impairments or inability to provide informed consent.

The study was approved by the Medical Ethics Committee Territoriale 3 (ID3924). Informed consent was obtained from all participants. The study protocol adhered to the ethical guidelines of the

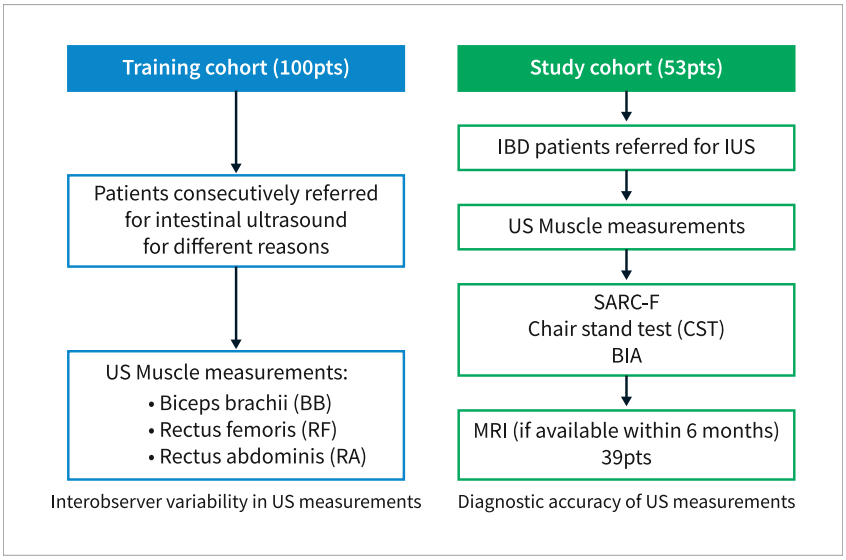

FIGURE 1 Study flow-chart. The *training cohort* included 100 patients and the *study cohort* 53 patients.

1975 Declaration of Helsinki (6th revision, 2008) as approved by the institution's human research committee.

Sarcopenia screening tests

We assessed the performance of the SARC-F questionnaire and CST at enrollment. The former is a widely accepted self-reported questionnaire with 5 parameters (Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls), each scored from 0 to 2.[21] SARC-F scores ≥4 were considered to be at risk of sarcopenia.[21] The latter measures the time required for a patient to stand up from a seated position 5 times without using the arms, over a 30-s interval, with decreased muscle performance defined according to the proposed cutoffs.[22]

Bioelectrical impedance analysis

BIA, a readily available and portable device, estimates muscle mass based on whole-body electrical conductivity. It uses a conversion equation calibrated with a reference of DXA-measured lean mass in a given population and is recognized by several international consensus statements for identifying sarcopenia.[4,23]

BIA allows an accurate estimate of the Appendicular Skeletal Muscle Index (ASMI) and the Free Fatty Mass Index (FFMI), both acknowledged measures of skeletal muscle mass. ASMI represents the sum of the four-limb muscle masses (ASM) adjusted for body size using height squared[24] and is often used as a surrogate marker for sarcopenia.[4] To measure ASM, BIA uses the Sergi equation calibrated with a reference of DXA-measured lean mass specific for the European population.[25]

FFMI is defined as free fat mass adjusted for body size using height squared and has shown a strong positive correlation with BIA- and DXA-measured ASMI, thus being a potential surrogate marker of ASMI.[26]

ASMI <7.05 and FFMI values <18 kg/m^2 in men and <15 and 5.85 kg/m^2 in women were used to diagnose sarcopenia.[26,27]

Body composition parameters were assessed using multifrequency BIA (Bodystat Quadscan 4000, Bodystat Ltd, UK) following the manufacturer's guidelines with regular calibration (at least twice per year). Resistance and reactance were measured at 50 kHz, while BIA impedance was determined at each frequency.

Muscle ultrasound

Muscle US was performed using a diagnostic US device (Philips Affiniti 70) equipped with a linear probe operating at 18–25 MHz. Two independent operators (SM, LP), blinded to each other and to patient clinical, biochemical, and histological data, conducted each measurement to ensure precision and reliability and to assess inter- and intra- observer variability.

Three superficial easily measured muscles were assessed: the biceps brachii (BB) and rectus femoris (RF), both appendicular muscles, and the rectus abdominis (RA), an axial muscle. These measurements adhered to the recommendations of SARCopenia through UltraSound (SARCUS) working group.[15]

Similar to BIA and MRI measurements, an USMI was defined for sarcopenia detection/prediction. USMI represented the sum of RF, RA, and BB thickness measurements divided by the square of the patient's height to mitigate the impact of anthropometric parameters on individual muscle measurements (Figure 2).

MRI analysis

We included diagnostic MRI examinations performed within 6 months of study enrolment, comprising both magnetic resonance enterography (MRE) and superior or inferior MRI. Most patients underwent abdominal examination on a 1.5 T magnet (Ingenia, Philips Healthcare, The Netherlands), using a 16-channel phased-array body coil. To assess sarcopenia, the images were then transferred to an image processing station (Philips Brilliance Workspace, Philips Healthcare, The Netherlands) where a transverse unenhanced T2-weighted image at the level of vertebra L3, with fully visible transverse processes, was selected. In cases where L3 was not available, the image was identified at the L5 level using a sagittal or coronal image. Two experienced radiologists (DG, DI), who were blinded to clinical and laboratory parameters, evaluated the MRI images. Muscle mass was assessed by measuring RA thickness 1 cm above the umbilicus on the right side, the areas of the right and left psoas muscle area (PMA), and the total muscle area (TMA). The latter included the psoas, para-spinal muscle, quadratus lumborum, transversus abdominis, external and internal oblique, and rectus abdominis muscles measured on transverse images at either L3 or L5.[28]

The measurement of the MR-skeletal muscle index (SMI) at the level of L3 by MRI is an accepted method for diagnosing sarcopenia.[4] While an MR-SMI cutoff of 50 cm^2/m^2 is considered diagnostic for sarcopenia in male cirrhotic patients (39 cm^2/m^2 for females),[29] specific cutoffs for patients with IBD are currently lacking.

Statistical analysis

The statistical analysis was conducted using MedCALC and PRISM software.

Results are given as median values and ranges unless otherwise stated. The data were analyzed using nonparametric tests: Friedman's test followed by Dunn's multiple comparison test, Wilcoxon's test for intragroup comparisons, and Mann-Whitney's test for intergroup comparisons. Chi-square and Fisher's exact tests were

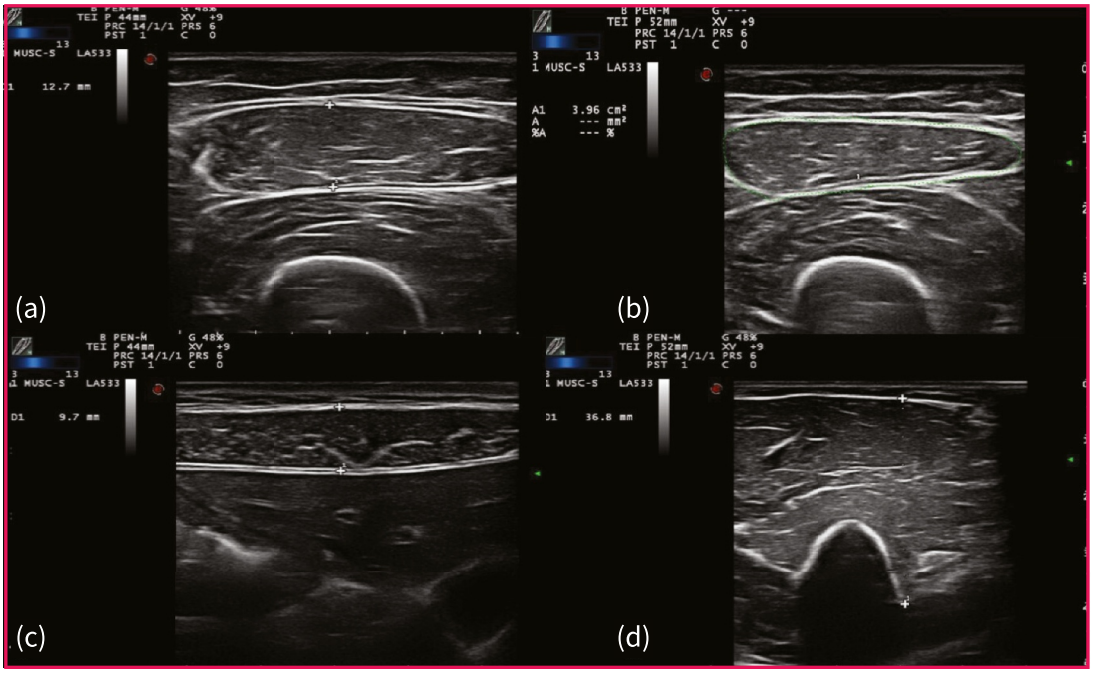

FIGURE 2 Muscle US measurement. The following measurements were made with the patient lying supine on a bed: RF muscle thickness (a) and cross-sectional area (b) at 50% distance between the spina iliaca anterior superior and the upper pole of the patella, with the knee flexed at 10°; RA muscle thickness (c) 1 cm above the umbilicus on the right side of the linea alba, during a deep inspiration; BB muscle thickness (d) on the dominant side was measured with the patient in the supine position at 50% distance between the greater tubercle of the humeral head and the elbow crease. Individual values of each operator, as well as the mean values between the two operators were collected.

used to compare frequencies and percentages. The Kruskal–Wallis test was applied to compare continuous variables among the groups.

Spearman's rank correlation coefficient (rS) was used to assess the correlation of each US measurement with the disease activity index, SARC-F score, ASMI, and specific MRI evaluation parameters.

Interrater reliability (IRR) in ultrasound measurements was assessed using the intraclass correlation coefficient (ICC).[30]

Additionally, we compared the Receiver Operating Characteristic (ROC) curves of US and MRI to assess the diagnostic performance of each method in comparison to BIA. ROC curves were compared using De Long's test. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and positive and negative likelihood ratios (LR+, LR−) were reported.[31] The maximum Youden index value determined the optimum cutoff point for distinguishing individuals with sarcopenic muscle mass.

Concordance between ASMI and FFMI was assessed using the Coen Kappa coefficient.[32] A p value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 153 patients participated in the study, with 100 in the *training cohort* and 53 in the *study cohort*. In the *study cohort*, the male-to-female ratio was 1.21, with a median age of 49 years (interquartile range [IQR] 32–66), and the median BMI was 23 Kg/m^2 (IQR 20–27). Among the *study cohort* patients, 34 (64.2%) had CD, while 19 (35.8%) had UC.

Training cohort

The training cohort comprised 100 consecutive adult patients, including both IBD and non-IBD individuals. They had a median age of 52 years (IQR 36–67) and a male-to-female ratio of 1.25. The median BMI was 24.5 kg/m^2 (IQR 21–28). Among the patients in this cohort, 56 had IBD, with 32 (57.1%) CD and 24 (42.9%) UC. The remaining 44 non-IBD patients underwent intestinal US for several gastrointestinal symptoms such as dyspepsia, irritable bowel syndrome, and celiac disease.

In the training cohort, the inter- and intra- operator agreement for US muscle measurements was excellent, with both single and mean ICC exceeding 0.95. The highest inter-observer agreement values were observed for RF CSA, reaching 0.97 for single ICC and 0.98 for mean ICC, giving reason for the feasibility and reliability of US muscle measurements.

Study cohort

Demographic and clinical characteristics of the study cohort are summarized in Table 1.

TABLE 1 Baseline characteristics of the "study cohort".

	Variable	Total patient [N = 53]
Patient characteristics	Age (years), median [IQR]	49 [32–66]
	Sex (male), *N* [%]	29 [54.7%]
	BMI (Kg/m^2), median [IQR]	23 [20–27]
	Inpatients, *N* [%]	7 [13.2]
IBD characteristics	Disease duration (years), median [IQR]	8 [3–13]
	Disease type (Crohn's Disease), *N* [%]	34 [64.2]
	UC extent, *N* [%]	
	• Proctitis	3 [6.1]
	• Left-sided	2 [4.1]
	• Extensive	13 [26.5]
	CD localization, *N* [%]	
	• L1	7 [20.6]
	• L2	3 [8.8]
	• L3	16 [47.1]
	• L4	0 [0]
	• L1 + L4	4 [11.8]
	• L3 + L4	4 [11.8]
	CD behavior, *N* [%]	
	• B1	12 [35]
	• B2	12 [35]
	• B3	10 [30]
	Clinical disease activity, *N* [%]	
	• Remission	31 [63]
	• Mild	12 [18.4]
	• Moderate	10 [18.9]
	• Severe	0 [0]
	Ongoing treatment, *N* [%]	
	• None	3 [5.6]
	• 5-ASA	10 [18.9]
	• AZA/6-MP	1 [1.9]
	• Biologics	32 [60.4]
	• Small molecules	2 [3.8]
	• Steroid	5 [9.4]
Biochemical characteristics	CRP (mg/dL), median [IQR]	0.29 [0.131.83]
	Calprotectin (mcg/g), median [IQR]	855 [107–1189]
	Hemoglobin (g/dL), median [IQR]	14 [12–15]
	WBC (x10^9/L)	7055 [5508–9150]
	Folate (ng/mL), median [IQR]	10 [6–40]
	Vitamin B12 (pg/mL), median [IQR]	360 [235–447]
	Ferritin (mg/dL), median [IQR]	53 [34–91]

Abbreviations: 6-MP, 6-Mercaptopurine; AZA, Azathioprine; BMI, body mass index; CD, Crohn's disease; CRP, C-reactive-protein; UC, ulcerative colitis.

The study cohort comprised 53 patients with IBD, with a male-to-female ratio of 1.21 and a median age of 49 years (IQR 32–66). The median BMI was 23 kg/m^2 (IQR 20–27). Among the patients in this cohort, 34 (64.2%) had CD, while 19 (35.8%) had UC.

(1) Sarcopenia prevalence according to BIA

According to the latest BIA cutoffs, the prevalence of sarcopenia in the *study cohort* was 50%, with a median ASMI of 6 (IQR 5.6–7.2). ASMI and Fat-Free Mass Index (FFMI) exhibited a strong correlation (rS 0.85, $p < 0.001$), with substantial concordance ($k = 0.76$).

(2) Sarcopenia US accuracy

Using BIA ASMI cutoffs of 7.05 and 5.85 kg/m^2 for men and women, respectively, as recently reported,[27] the ROC curve analysis of US thickness measurements of RA and BB demonstrated good accuracy.

Among the measurements of each muscle, RA thickness showed the best AUROC of 0.85 ($p < 0.0001$), followed by BB and RF with an AUROC of 0.8 each ($p < 0.0001$), and RF CSA with an AUROC of 0.76 ($p = 0.0001$). Lastly, USMI also exhibited good accuracy, with a robust AUROC of 0.81 ($p < 0.0001$) (Figure 3).

Based on the highest Youden values while optimizing for sensitivity, we determined optimal sarcopenia diagnostic cutoffs for each US measurement (Table 2). According to these US cutoffs, the prevalence of sarcopenia in the *study cohort* was 60%, 58%, and 60% for RA, BB, and RF thickness, and 61% and 69% for RF CSA and USMI.

(3) Sarcopenia MRI accuracy and MRI-US agreement

Among the 53 patients in the *study cohort*, 39 had undergone MRI in the previous 6 months: 22 had MRE and 17 had upper or lower abdominal MRI. Median time from US to MRI examination was of 2 months (IQR 0–3). Analysis of the ROC curve from MR-SMI and RA thickness showed a good accuracy compared to BIA, with AUROC values of 0.8 ($p < 0.0001$) and 0.84 ($p < 0.001$), respectively. In contrast, psoas CSA evaluated by MRI yielded an AUROC of 0.6 ($p = 0.28$) (Figure 4).

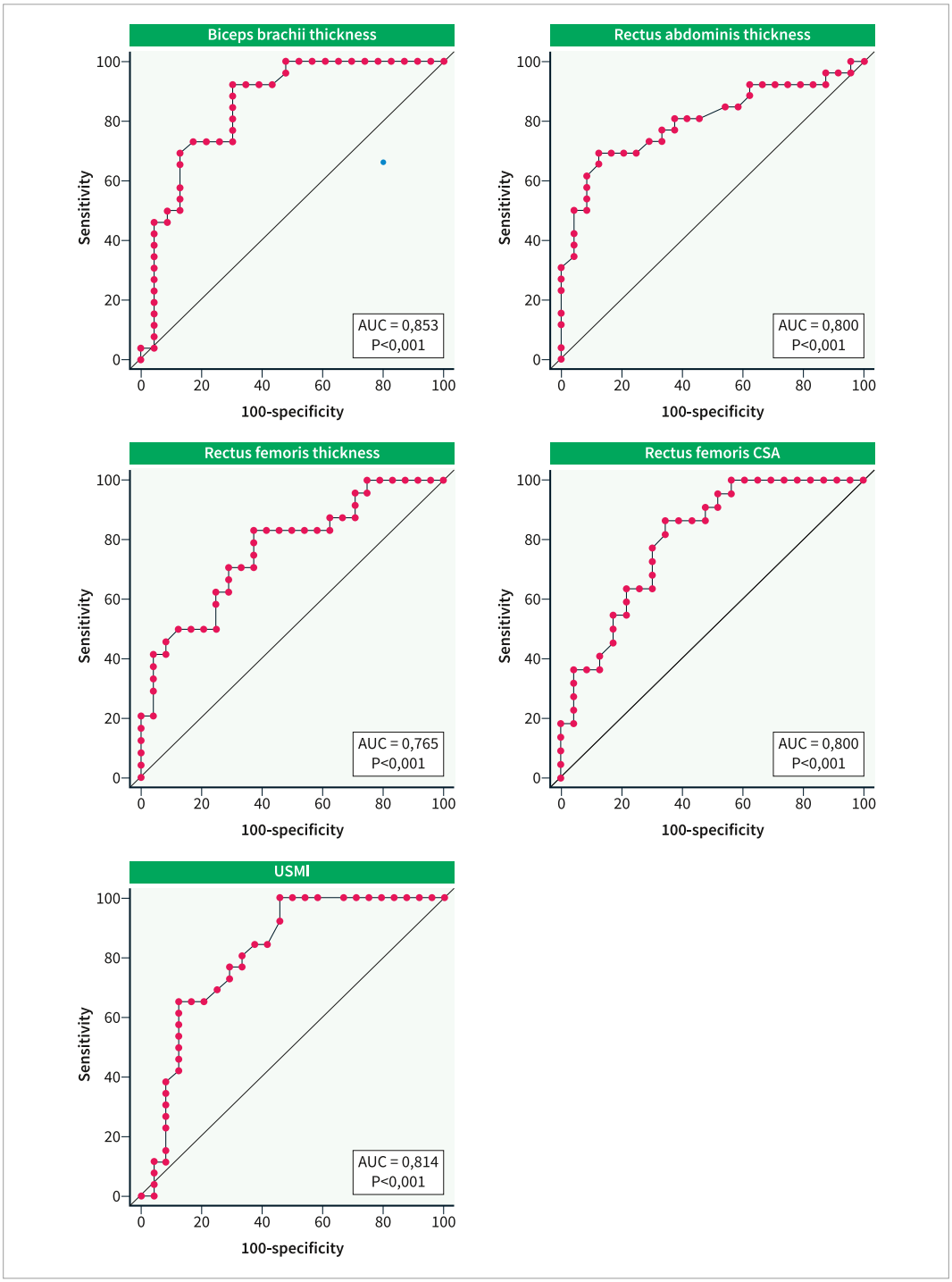

FIGURE 3 Performance of US muscle evaluation in the assessment of sarcopenia, when compared to BIA.

The agreement between US and MRI measurements of RA was excellent (ICC 0.96), and no statistical significance was observed when comparing US and MRI AUROCs ($P = 0.69$) (Figure 5).

(4) SARC-F and CST

Results of SARC-F and CST were compared with BIA. SARC-F exhibited poor diagnostic accuracy with an AUROC of 0.54 ($p = 0.5$). Similarly, CST demonstrated suboptimal diagnostic performance with an AUROC of 0.76 ($p = 0.001$). For CST, a cutoff of 13 had a sensitivity and specificity of 78% and 62%, respectively, with a LR + of 2.04 and LR – of 0.36.

ROC curves comparison between SARC-F and USMI and BIA showed a significantly better AUROC ($p = 0.001$) for USMI compared with SARC-F, while no significant difference was observed between CST and USMI ($p = 0.5$) (Supplementary Figure S1).

TABLE 2 Ultrasound sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+ and LR−) and diagnostic cutoffs for sarcopenia at the Youden index (J).

Muscle US parameter	J	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR−	Cutoff at J
Biceps brachii thickness, mm	0.62	92	70	75	90.8	3	0.11	36.25 mm
Rectus abdominis thickness, mm	0.56	80	62.5	68	75.6	5.5	0.35	8.7 mm
Rectus femoris thickness, mm	0.45	83.3	62.6	69.1	79	2.22	0.27	12.9 mm
Rectus femoris CSA, cm^2	0.52	86	65	71.1	82.3	2.5	0.21	5.7 cm^2
USMI, mm/h^2	0.54	100	54.17	68.5	100	2.18	0	21.9 mm/h^2

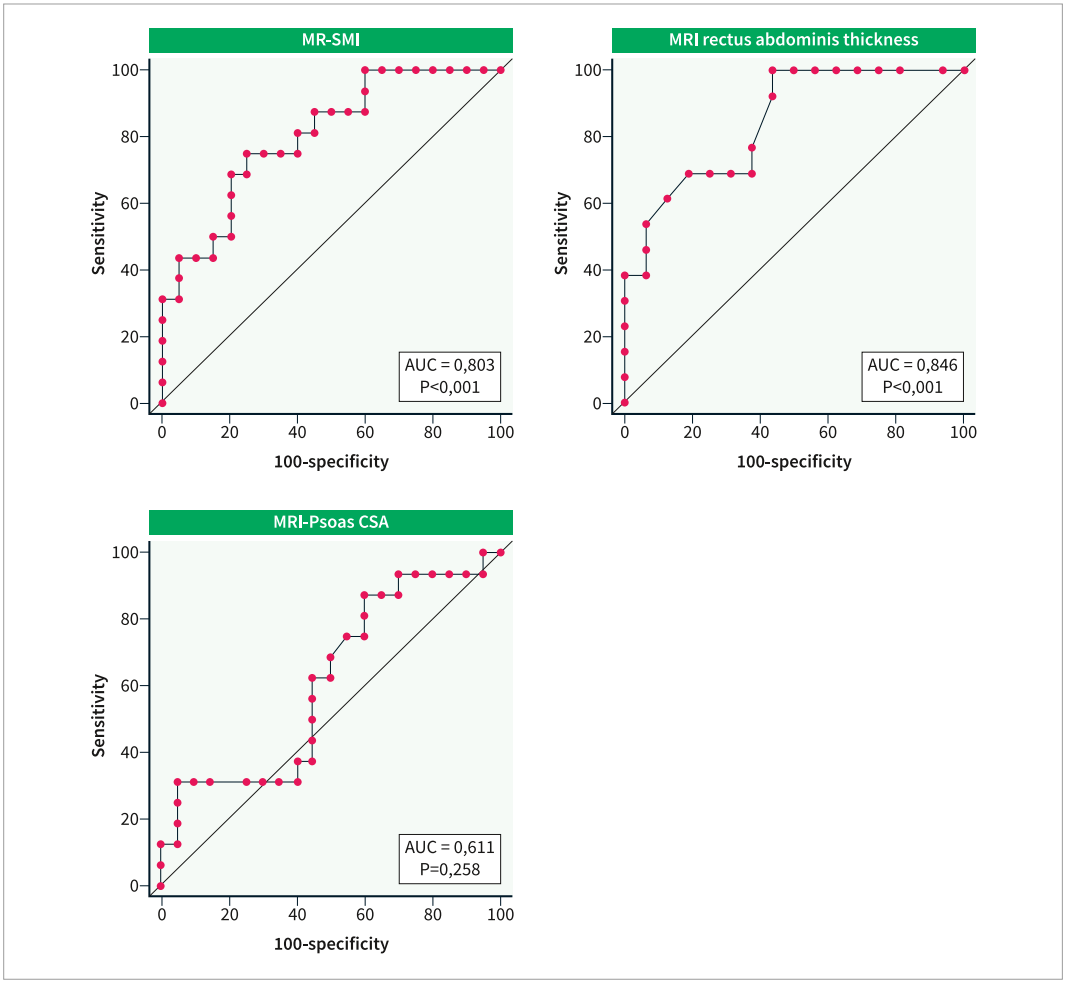

FIGURE 4 Performance of MRI muscle evaluation in the assessment of sarcopenia, when compared to BIA.

(5) Correlation of US, MRI, and BIA with disease activity and biochemical parameters

Correlations between disease activity (pMAYO and HBI) and specific US, MRI, and BIA parameters were assessed. US measurements showed weak to moderate correlations with disease activity, with RA thickness and USMI having moderate correlations (rS −0.53 and −0.52, $p < 0.0001$). Weak correlation with disease activity were observed for BB thickness, RF thickness, and CSA (rS −0.41, −0.49, −0.41; $p < 0.01$).

MRI measurements demonstrated weak correlations with disease activity (rS −0.44, −0.41, −0.38; $p < 0.01$), with no correlation observed for psoas muscle CSA (Rs −0.15, p = NS).

Moreover, ASMI and FFMI showed weak and no correlations, respectively (−0.39 and −0.23; $p < 0.01$). As for biochemical parameters, complete blood count (CBC) and CRP were available for all patients (100%), while fecal calprotectin data were accessible for half of the patients (50%). None of the biochemical parameters exhibited significant correlations with US, MRI, or BIA measurements. Screening for malnutrition using the MUST identified varying risk

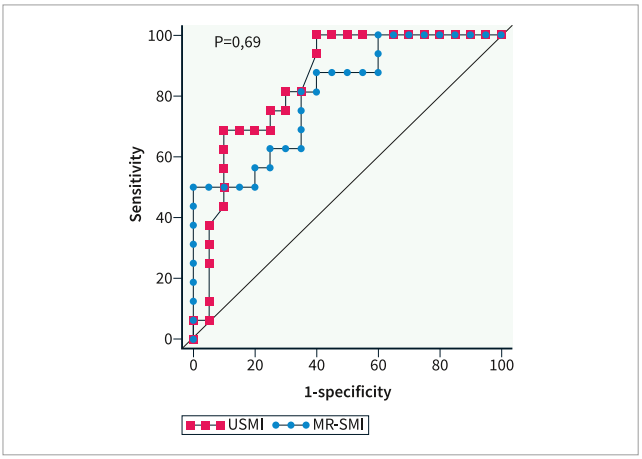

FIGURE 5 ROC curve comparison between USMI, MRI-SMI, and BIA.

levels within the study population: low risk in 35 patients (66%), medium risk in 12 patients (22.7%), and high risk in 6 patients (11.3%). All patients at high-risk of malnutrition were sarcopenic, while 18 (66%) patients with sarcopenia were at risk for malnutrition, of which only 6 (22%) were at high risk for malnutrition. According to the US cutoffs, the prevalence of sarcopenia was 60% when using the RA measurement and 69% when using the USMI measurement.

DISCUSSION

This prospective study aimed to evaluate the diagnostic accuracy of US in assessing sarcopenia in patients with IBD and to compare it with other diagnostic tools. Our findings suggest that US muscle measurements are a reliable, rapid, and accurate method to diagnose sarcopenia. Consistent with some literature reports,[1,33] study results revealed a high prevalence of sarcopenia (50%) among patients with IBD, thus emphasizing the importance of assessing muscle mass and function in this population.

In this study, we compared US measurements of specific muscles (BB, RA, RF) with BIA, which is a recognized reference diagnostic tool.[4] US demonstrated good diagnostic accuracy in detecting sarcopenia when compared to BIA, with high AUROC values. Inter-rater and intra-rater reliability was excellent (ICC >0.95) for each muscle measurement. We also established optimal cutoff values for US measurements to diagnose sarcopenia in IBD patients, including the new US Muscle Index (USMI), providing reliable prediction models for sarcopenia detection. These cutoffs can help clinicians to early recognize sarcopenic patients more accurately. Analogously to the ASMI, FFMI, and MR-SMI, we proposed the first US muscle index score (USMI) for sarcopenia prediction to overcome the influence of anthropometric parameters on single muscle measurements. ROC curve analysis identified a USMI cutoff of 21.9 mm/h^2 as an optimal diagnostic tool for sarcopenia, with a sensitivity of 100%. This achievement is particularly noteworthy as none of the other diagnostic methods have tested their accuracy specifically within the context of IBD, and therefore, no specific cutoff values exist for MRI, CT scans, or even BIA, which we have used as the reference standard in this study. While BIA was chosen as the reference standard due to its ease of availability, user-friendliness, cost-effectiveness, and avoidance of ionizing radiation exposure (particularly important in the case of young IBD patients), it does have inherent limitations, including the absence of specific cutoff values tailored to IBD patients.

The potential to early diagnose IBD patients as being sarcopenic using US offers an attractive solution to increase awareness of sarcopenia and facilitate timely nutritional interventions. Furthermore, this study observed an excellent agreement between US and MRI measurements of rectus abdominis, indicating that US can be a reliable alternative to MRI in assessing muscle parameters in IBD patients. Despite the relatively limited number of available MRI examinations, AUROCs from MR-SMI and USMI showed similar accuracy in sarcopenia detection ($p = 0.69$), suggesting concordance between US and MRI assessment of muscle mass.

Current gold standard screening tools such as SARC-F and CST, and HGS, originally validated for geriatric populations, demonstrated limited diagnostic performance in our relatively young IBD cohort. In the IBD population, data on SARC-F and CST are not available, whereas decreased HGS has recently been associated with an increased risk of hospitalization.[34]

In our study, SARC-F exhibited low sensitivity, of 33% and 37% when compared to BIA and US, respectively, while CST performed slightly better but still lacked ideal sensitivity and specificity (respectively of 78% and 62% when compared to BIA, using a cutoff of 13). These results highlight the need for more accurate methods than SARC-F even for sarcopenia screening and not only to confirm the diagnosis of sarcopenia in IBD, such as US or BIA. The lack of correlation between SARC-F and sarcopenia in our study may be attributed to the relatively young age of our *study cohort* as the tool was originally validated for geriatric populations.[21] On the other hand, US measurements showed not only diagnostic accuracy but also the potential for use as a screening tool. In fact, US measurements exhibited better sensitivity compared to SARC-F and CST, suggesting that US could be a valuable screening test for sarcopenia in the IBD population. This potential for early and accurate detection with US could lead to timely interventions and improved patient outcomes.

The high prevalence of sarcopenia in patients with IBD, also observed in our study, might reflect the underlying chronic inflammatory status. Chronic inflammation can lead to the release of specific factors (i.e. tumor necrosis factor, interleukin-6, interleukin-1) that ultimately promote muscle wasting through the activation of intracellular pathways and the reduction of several anabolic hormones such as insulin-like growth factor-1.[8,11]

In patients with IBD, several factors contribute to an elevated risk of both sarcopenia and malnutrition. These factors include chronic inflammation, alterations in nutrient absorption, reduced appetite, and the catabolic effects of the disease itself. Surprisingly, our study revealed that sarcopenia can manifest independently of

malnutrition in IBD patients. In fact, approximately 34% of sarcopenic patients in our cohort did not exhibit signs of malnutrition. This discovery challenges the traditional notion that sarcopenia primarily occurs because of malnutrition, where the depletion of essential nutrients, including amino acids, leads to muscle tissue breakdown. This observation underscores the importance of independently assessing both sarcopenia and malnutrition in IBD patients to ensure comprehensive patient care.[35] Rather than being a mere complication of malnutrition, sarcopenia may exist as a pre-existing or independent condition in this population. Both sarcopenia and malnutrition can significantly impact clinical outcomes and reduce the overall quality of life for individuals with IBD.[1–3,8]

In line with this, our study explored the relationship between muscle parameters (US, MRI, and BIA) and disease activity in IBD patients. US measurements, particularly RA thickness and USMI, demonstrated a moderate negative correlation with disease activity, suggesting that as disease activity increases, muscle parameters tend to decrease.

However, no significant correlation was found between muscle parameters and biochemical markers, such as C-reactive protein (CRP), hemoglobin, or fecal calprotectin, indicating that muscle loss may be more closely related to disease activity than systemic inflammation.

The findings of this study have important clinical implications for managing patients with IBD. Identifying sarcopenia in IBD patients is crucial as it can impact their overall health, including disease progression and response to treatment. Our results suggest that US can be a valuable tool for assessing sarcopenia in clinical practice, offering a reliable and cost-effective alternative to MRI. Additionally, the study provides cutoff values that can aid clinicians in accurately diagnosing sarcopenia.

The major strength of this study is that it is the first to assess the role of US in diagnosing sarcopenia in IBD patients and to compare it with the current diagnostic reference-standard.

However, it has limitations, including a relatively small sample size, single-center design, lack of long-term follow-up to assess the impact of sarcopenia on disease outcomes, and absence of quality muscle measurements such as those suggested by the SARCUS working group recommendations (pennation angle, fascicle length, echo-intensity, muscle stiffness, contraction potential, and microcirculation).[15]

Additionally, the lack of correlation between MRI parameters and clinical disease activity indices might be due to extended intervals between the exams. While we accepted a predefined condition of MRI being performed up to 6 months before the US, the median time from US to MRI in our study was considerably shorter, being of 2 months. This relatively short time interval between US and MRI assessments helps reduce the potential impact of time-related variability on our comparative analysis.

Finally, another weakness point is that we used BIA cutoffs from Asian populations, which may not be entirely reproducible in the European population. Larger multicentric cohorts with longer follow-up periods are needed to validate these findings and explore their clinical significance further.

In conclusion, this study contributes valuable insights into the assessment of sarcopenia in IBD patients. It highlights the potential of US as a reliable diagnostic tool and suggests that muscle loss is associated with disease activity. These findings could inform clinical practice and guide future research aimed at improving the management of sarcopenia in IBD patients. Further studies with larger cohorts and longer follow-up periods are needed to validate these findings and explore their clinical significance in greater detail.

AUTHOR CONTRIBUTIONS

Sara Massironi conceived the work. Sara Massironi and Giacomo Mulinacci participated in the design, execution, analysis, and interpretation of the study. Giacomo Mulinacci, Lorena Pirola, Camilla Gallo, and Sara Massironi participated in the execution of the study and data collection. Giacomo Mulinacci, Chiara Viganò and Alice Laffusa carried out the literature review and were involved in patient recruitment and clinical assessments. All authors provided critical feedback and helped shape the research, analysis, and manuscript. Sara Massironi, Pietro Invernizzi, and Silvio Danese provided expertise in critical revision of the final version of the paper.

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CONFLICT OF INTEREST STATEMENT

Silvio Danese reports consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Enthera, Ferring Pharmaceuticals Inc., Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB Inc., and Vifor. There are no financial disclosures or conflicts of interest among the other authors.

DATA AVAILABILITY STATEMENT

The data used in this study, including patient characteristics, diagnostic measurements, and outcomes, are available upon request from the corresponding author. Access to the data will be subject to any applicable ethical and legal requirements to protect patient privacy and confidentiality.

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SUPPORTING INFORMATION

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