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Comparison of ultrasound speed-of-sound of the lower extremity and lumbar muscle assessed with computed tomography for muscle loss assessment

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Abstract

To compare the speed of propagation of ultrasound (US) waves (SoS) of the lower leg with the clinical reference standard computed tomography (CT) at the level of lumbar vertebra 3 (L3) for muscle loss assessment. Both calf muscles of 50 patients scheduled for an abdominal CT were prospectively examined with ultrasound. A plexiglas-reflector located on the opposite side of the probe with the calf in between was used as a timing reference for SoS (m/s). CT measurements were performed at the level of L3 and included area (cm^2) and attenuation (HU) of the psoas muscle, abdominal muscles, subcutaneous fat, visceral fat and abdominal area. Correlations between SoS, body mass index (BMI) and CT were determined using Pearson's correlation coefficient. Based on reported CT sarcopenia threshold values, receiver operating characteristic (ROC) analysis was performed for SoS. Inter-examiner agreement was assessed with the median difference, inter-quartile range (IQR) and intraclass correlation coefficients. SoS of the calf correlated moderately with abdominal muscle attenuation ($r = 0.48$; $P < .001$), psoas muscle attenuation ($r = 0.40$; $P < .01$), abdominal area ($r = -0.44$; $P < .01$) and weakly with subcutaneous fat area ($r = -0.37$; $P < .01$). BMI correlated weakly with psoas attenuation ($r = -0.28$; $P < .05$) and non-significantly with abdominal muscle attenuation. Normalization with abdominal area resulted in moderate correlations with abdominal muscle area for SoS ($r = 0.43$; $P < .01$) and BMI ($r = -0.46$; $P < .001$). Based on sarcopenia threshold values for skeletal muscle attenuation (SMRA), area under curve (AUC) for SoS was 0.724. Median difference between both examiners was -3.4 m/s with IQR $= 15.1$ m/s and intraclass correlation coefficient $= 0.794$. SoS measurements of the calf are moderately accurate based on CT sarcopenia threshold values, thus showing potential for muscle loss quantification.

Abbreviations: AUC = area under the curve, BMI = body mass index, CT = computed tomography, L3 = lumbar vertebra 3, MRI = magnetic resonance imaging, SMA = skeletal muscle area, SMI = skeletal muscle index, SMRA = skeletal muscle (radiation) attenuation, SoS = speed of sound, US = ultrasonography.

Keywords: adipose tissue, skeletal muscle, tomography, ultrasonography, x-ray computed tomography

1. Introduction

Based on the definition of the European Working Group on Sarcopenia in Older People, sarcopenia is defined by the presence of both low muscle mass and low muscle function.[1] It is not only associated with falls and fractures in the elderly,[2] but also with an increased risk for other diseases, such as pneumonia.[3]

Muscle loss can be detected with several different methods. Body mass index (BMI) is a widely used anthropometric index, but it does not precisely assess the body fat amount.[4] Bioelectrical impedance analysis presents an established method to assess low muscle mass, yet lacks standardization.[5] Imaging techniques that aid in quantifying muscle loss include dual x-ray absorptiometry, computed tomography (CT) as well as magnetic resonance imaging (MRI).[6]

Computed tomography presents a reference standard for the assessment of muscle mass.[7] Skeletal muscle sarcopenia cut-off values have been reported for the level of the lumbar vertebra 3 (L3).[7,8] Low skeletal muscle area (SMA, cm^2) on the lumbar level, which shows a strong correlation with whole body muscle mass,[9] has been related with a poor clinical outcome [10] in patients undergoing chemotherapy [11,12] or surgery.[13,14] Skeletal muscle index (SMI, cm^2/m^2), a height-adjusted measure of SMA (SMI = SMA/height[2]), presents a measure for relative muscle mass [8] with prognostic value in oncologic diseases.[15] Skeletal muscle (radiation) attenuation (SMRA, HU), which is a

measure of the fat content in muscle[16] and related to physical functioning,[17,18] has been recognized as an important prognostic factor in a screening population[19] and in oncologic patients.[20,21] Psoas index, defined as psoas muscle area divided by body surface area[22] has been highlighted due to its predictive potential in patients with aortic valve disease.[22]

Sonographically assessed Speed of Sound (SoS) is a quantitative imaging biomarker, which measures the speed of longitudinal wave propagation.[23] The Speed of Sound depends on the medium, in which ultrasound waves propagate. The SoS value of fat (1440 m/s) is markedly lower than that of other body tissues, such as muscle (1585 m/s).[24] Several research studies have demonstrated the potential of SoS to detect fat content in tissue, such as for fatty muscular degeneration,[23] breast density classification[25] and fatty liver disease.[26] Ruby et al. found very strong correlations between SoS and the total fat fraction of the same lower leg muscle volume section assessed with Dixon MRI.[27] Increased fat fraction has been found to be associated with decreased physical function of the leg muscles,[28] which has been identified as an important risk factor for falls in elderly.[29]

The aim of this study was to compare two surrogate parameters, sonographic SoS of the lower leg as a measure of physical function of the lower extremity with the clinical reference standard CT of the abdomen at the level of L3 for muscle loss assessment.

2. Materials and methods

2.1. Study design

This prospective, single-institution study has been carried out in accordance with "The Code of Ethics of the World Medical Association" (Declaration of Helsinki) for experiments involving humans. It has been approved by the institutional review board and the local ethics committee. Written informed consent was obtained from all patients. Inclusion criterion was a scheduled appointment for the same CT examination, which was specifically designed for a follow-up exam for patients having undergone endovascular aortic repair. Both calf muscles of 50 consecutive patients (40 males, 10 females) that underwent this particular CT examination (reference test) were prospectively examined with ultrasound on the same day to assess the SoS (index test). Exclusion criteria included pathologies of the two

examined anatomic regions, psoas muscle and lower legs. One male patient was excluded due to a psoas abscess, which did not allow evaluation of the psoas area. Semi-automatic segmentation of the body compartments was performed on the CT data. Both the area and attenuation (CT) values of the abdominal muscles at the level of L3 were compared to the calculated SoS (US), body weight (U-018, Tanita Europe, Germany), height and BMI. The validated Tegner activity score form was used for activity assessment through completion of a questionnaire by all participants.[30]

2.2. Computed tomography (CT)

2.2.1. Data acquisition. All examinations were performed on a third-generation dual-source CT system (SOMATOM Force, Siemens Healthineers, Forchheim, Germany) equipped with integrated circuit detectors (Stellar Infinity, Siemens Healthineers, Forchheim, Germany). All patients received 70 ml Ultravist 370 mg (Bayer, Switzerland) injections intravenously and arterial and venous phase images were acquired. All evaluations were performed using the image data of the venous phase, which was consistently scanned with 120 kV. Collimation was 96×0.6 mm. Image reconstruction was performed utilizing advanced model-based iterative reconstruction (ADMIRE, strength level 3, Siemens Healthineers, Forchheim, Germany) with a slice thickness of 2 mm at an increment of 1.6 mm and a medium soft tissue kernel (BV 36). All CT images were anonymized and transferred to an external workstation (Multi-Modality Workplace, Siemens Healthineers, Forchheim, Germany) for further analysis.

2.2.2. Quantitative/qualitative analysis. The CT system was calibrated with phantoms to provide absorption coefficients in Hounsfield units (HU). The L3 slice (Fig. 1a) was selected by determining lumbar vertebra 5 (L5) at the lumbosacral junction and counting from there utilizing ImageJ.[31] If there was a lumbosacral anomaly, the thoracic vertebra 1 (Th1) was determined and counting started from there. Fat values were then binarized in the L3 slice with an attenuation range between [−190 HU, −30 HU][32,33] and muscle values were binarized with an attenuation range between [−29, 150 HU].[33,34] From the muscle map, the psoas muscle (red) and abdominal wall muscles (orange) were manually segmented using Paint (Microsoft Paint, Microsoft, NM, USA) (Fig. 1b). Similarly, from the fat
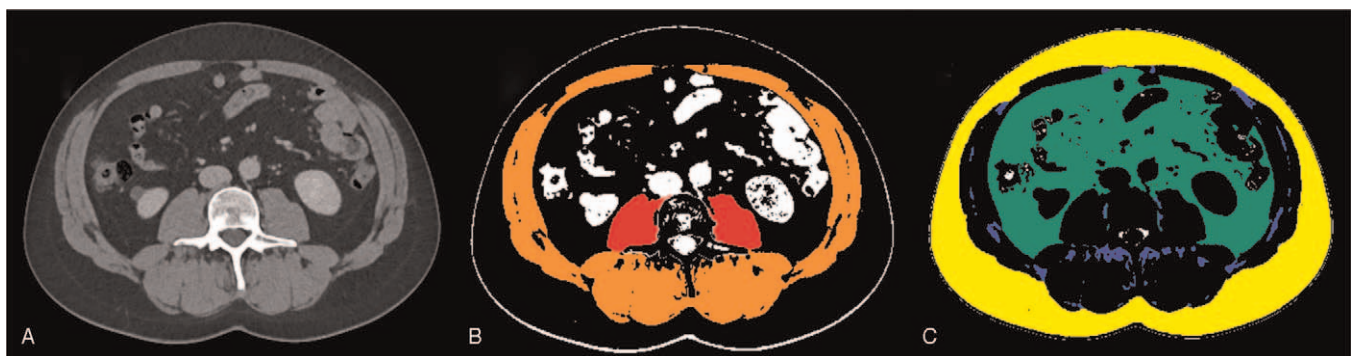
Figure 1. L3 slice segmentation: The L3 slice (A) was manually selected. Using this slice, fat values were binarized with an X-ray absorption range between [−190 HU, −30 HU] and muscle values were binarized between [−29, 150 HU]. Out of the muscle map, viscerae, bone and skin were manually excluded and the psoas muscle (red) and further abdominal muscles (orange) were segmented (B). Out of the fat map, subcutaneous fat (yellow), visceral fat (green) and intramuscular fat (blue) were segmented (C).

Figure 2. Speed of Sound (SoS) principle and measurement setup: A) Principle: The speed of sound (m/s) is calculated by assessing the sound wave propagation time (s) and the distance d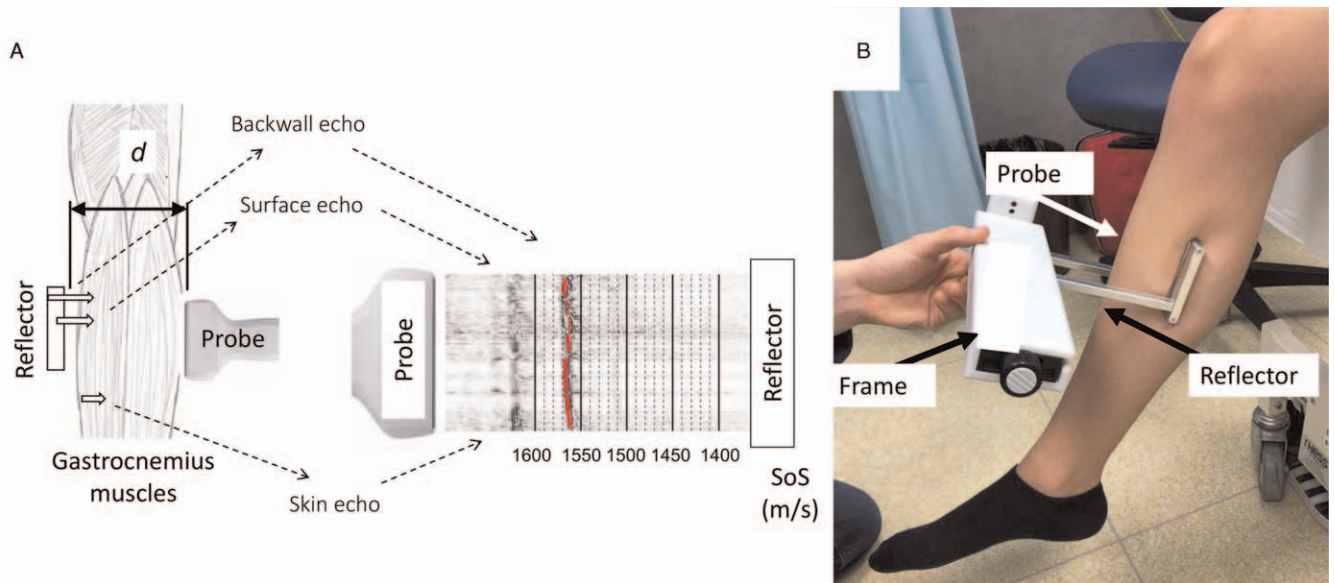 (m) between the probe and reflector. An automatic algorithm (red line) recognizes the backwall echo line and calculates the mean SoS. B) The reflector was located medial and the ultrasound probe lateral to the posterior calf. Both components are connected through a frame, from which the distance between the probe and the reflector can be read manually.

map, subcutaneous fat (yellow), visceral fat (green) and intramuscular fat (blue) were segmented (Fig. 1c). Morphological signal processing was used to automatically distinguish intramuscular fat in psoas with respect to intramuscular fat of other abdominal muscles. Intramuscular fat of psoas was defined as eight connected fat regions showing more boundary pixels connected to psoas than to other muscular regions. Surface area and attenuation values were calculated for the following parameters: "Abdominal," defined as all segmented (colorful in Fig. 1b,c) areas, "abdominal muscle" defined as all segmented muscle including psoas and any intramuscular fat, "psoas," defined as segmented psoas muscle area including intrapsoas fat, as well as subcutaneous and visceral fat.

2.3. Hand-held speed of sound ultrasound (SoS) – index test

Ultrasound measurements were performed by one examiner (L. R.) using a standard ultrasound machine (Paolus UF-760AG, Fukuda Denshi, Tokyo, Japan). A flat Plexiglas reflector served as a timing reference for the SoS (m/s) signals transmitted through the calf. It was placed in longitudinal direction on the medial calf at the height of maximum calf circumference (Fig. 2a,b). On the opposite lateral side of the calf, a handheld 5-12 MHz linear US probe (FUT-LA385-12P) was positioned. Ultrasound lotion (PolySonic, Parker Laboratories, Inc., Fairfield, US) was applied on the reflector and probe surfaces. We attached both probe and reflector to a positioning frame that allowed controlling the distance between the probe and reflector. The frame was adjusted to achieve contact between the ultrasound probe, calf and reflector. The measurements were performed in a sitting position, with the calf muscle in a resting state. An automatic algorithm performed the SoS readings.[35] Three repeated measurements were performed for each leg and the median of the six SoS segments was used for further evaluation. Probe, reflector and frame were completely removed from the calf after each

measurement. For 19 patients, three additional measurements of the right leg were performed by a second examiner (S.J.S.) following the measurements of examiner one to assess inter-examiner agreement. The first examiner was absent during these measurements to avoid a bias.

2.4. Muscle attenuation and mass threshold values

Reported muscle attenuation and mass threshold values for sarcopenia diagnosis (psoas index, skeletal muscle area, skeletal muscle index and skeletal muscle (radiation) attenuation) were used to assess the accuracy of SoS. Threshold values aided in the allocation into sarcopenic and non-sarcopenic groups. For psoas index (psoas area/ body surface area), we used the reported 25th percentile cutoff for sarcopenia, which was $9.09\,cm^2/m^2$ for men and $6.96\,cm^2/m^2$ for women.[22] Threshold values for skeletal muscle area (SMA) included $144.3\,cm^2$ for men and $92.2\,cm^2$ for women, for skeletal muscle index (SMI) $45.4\,cm^2/m^2$ for men and $34.4\,cm^2/m^2$ for women and for skeletal muscle (radiation) attenuation (SMRA) 38.5 HU for men and 34.3 HU for women [7]

2.5. Statistical analysis

We performed the statistical analysis with Matlab (2014a, The MathWorks Inc., Natick, MA, USA) and Medcalc (Ostend, Belgium). Continuous values were shown as means ± SD (standard deviation) and discrete values as medians and range. Pearson correlation r was calculated to assess correlations between SoS, BMI and CT parameters. The strength of the correlation was evaluated following Stewart,[36] with correlation coefficients between 0 to 0.19 considered as very weak, 0.20 to 0.39 as weak, 0.40 to 0.59 as moderate, 0.60 to 0.79 as strong and 0.80 to 1.00 as very strong. The strength of accuracy was rated according to,[37] with an area under the curve (AUC) greater than 0.9 considered as highly, 0.7 to 0.9 moderately and
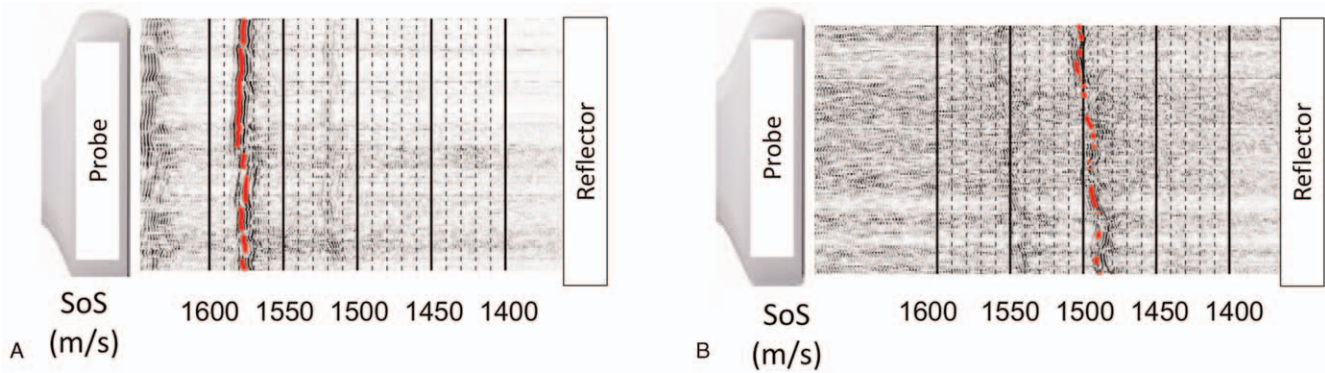
Figure 3. Exemplary Speed of Sound (SoS) images of a patient with high (mean = 1572 m/s) (A) and low (mean = 1503 m/s) (B) Speed of Sound (SoS) values are shown.

0.5 to 0.7 as lowly accurate. SoS values of sarcopenic and non-sarcopenic groups, based on reported threshold values for psoas index, SMA, SMI and SMRA, were compared for each parameter using Student t test. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance of SoS based on the threshold values of the four parameters. Inter-examiner agreement was assessed for 19 patients using the intraclass correlation coefficient[38] and the median difference including the inter-quartile range (IQR).

For SoS significance difference assessment between sarcopenic and non-sarcopenic patients, we used an unpaired t test. For significant correlation assessment ($r > 0$), we used the P values provided by corrcoef in Matlab. The P value was computed by transforming the correlation to create a t statistic having n-2 degrees of freedom, where n is the number of samples. For significant AUC assessment (AUC > 0), we used MedCalc Software Ltd (19.6.4, Ostend, Belgium), which calculates errors based on the DeLong method.[39] A two-tailed P value <.05 indicated statistical significance.

3. Results

3.1. Participants

Patients had a median age of 70 years (range 47–89 years), mean height of 173.6 ± 9.6 cm, weight of 81.7 ± 12.5 kg and BMI of 27.2 ± 4.5 kg/m^2.

3.2. US (index test) and CT (reference standard)

The mean examination time of SoS-US for both calf measurements, including three repetitions per leg, was 3 minutes, ranging from 2 to 4 minutes. A total of 357 (50 patients * 3 repeated measurements * 2 legs + 19 patients * 3 repeated measurements performed by examiner two) SoS segments were acquired. 349/357 segments (97.76%) were successful. For the remaining 8 segments, the signal to noise ratio (< 6 dB) was too small to visualize the reflector signal. For 312/357 segments (87,3%), the delineation algorithm was able to correctly identify the reflector and automatically measure SoS, while in 32/357 segments manual annotation (8.96%) was necessary. All 32 manually annotated segments suffered from low signal to noise ratio (<10 dB), with the automatic algorithm identifying an incorrect echo for 13/32 segments, and not converging to an echo in 19/32

segments. All 50 patients had at least 4 SoS segments available for fat quantification, with 44/50 having 6 segments available, 5/50 having 5 segments available and 1/50 having 4 segments available.

3.2.1. Ranges. Abdominal area, abdominal muscle and psoas muscle areas ranged from 496.3 to 1193.4 cm^2, 104.9 to 217.3 cm^2 and 11.3 to 31.9 cm^2, respectively. Attenuation values ranged from 0.9 to 50.6 HU for abdominal muscle and from 4.0 to 57.8 HU for psoas muscle. SoS ranged from 1497.9 to 1572.3 m/s. Exemplary SoS (Fig. 3) and CT (Fig. 4) images of a patient with a high median SoS (1572 m/s) (Fig. 3a) and large psoas area (24.26 cm^2) (Fig. 4a) as well as a second patient with a low median SoS (1503 m/s) (Fig. 3b) and a small psoas area (15.43 cm^2) (Fig. 4b) are shown.

3.2.2. Correlations between SoS and CT parameters. SoS correlated moderately with abdominal muscle ($r = 0.48$; $P < .001$) and psoas muscle ($r = 0.40$; $P < .01$) attenuation (Fig. 5, Table 1). Correlations were moderate for the comparison of SoS with abdominal area ($r = -0.44$; $P < .01$) and weak for SoS and subcutaneous fat area ($r = -0.37$; $P < .01$). No significant correlations were found for psoas muscle area, abdominal muscle area and visceral area compared to SoS. Normalization with abdominal area resulted in moderate and weak correlations for muscle area ($r = 0.43$; $P < .01$) and psoas area ($r = 0.39$; $P < .01$).

3.2.3. Correlations of BMI with SoS and CT. BMI correlated moderately ($r = -0.50$; $P < .001$) with SoS. BMI correlated weakly with psoas attenuation ($r = -0.28$; $P < .05$) and non-significantly with abdominal muscle attenuation. It correlated weakly with abdominal muscle ($r = 0.34$; $P < .05$) and psoas muscle area ($r = 0.31$; $P < .05$). BMI correlated very strongly with abdominal area ($r = 0.80$; $P < .001$), strongly with visceral ($r = 0.61$; $P < .001$), and moderately with subcutaneous ($r = 0.57$; $P < .001$) areas. Normalization with abdominal area resulted in a moderate correlation of abdominal muscle area ($r = -0.46$; $P < .001$) and a non-significant correlation of psoas muscle area with BMI.

3.2.4. Accuracy based on sarcopenia metrics. Out of the four metrics SMA, SMI, SMRA and psoas index, the SoS comparison between sarcopenic and non-sarcopenic patients was significant for SMRA ($P < .05$) based on the SMRA threshold values for
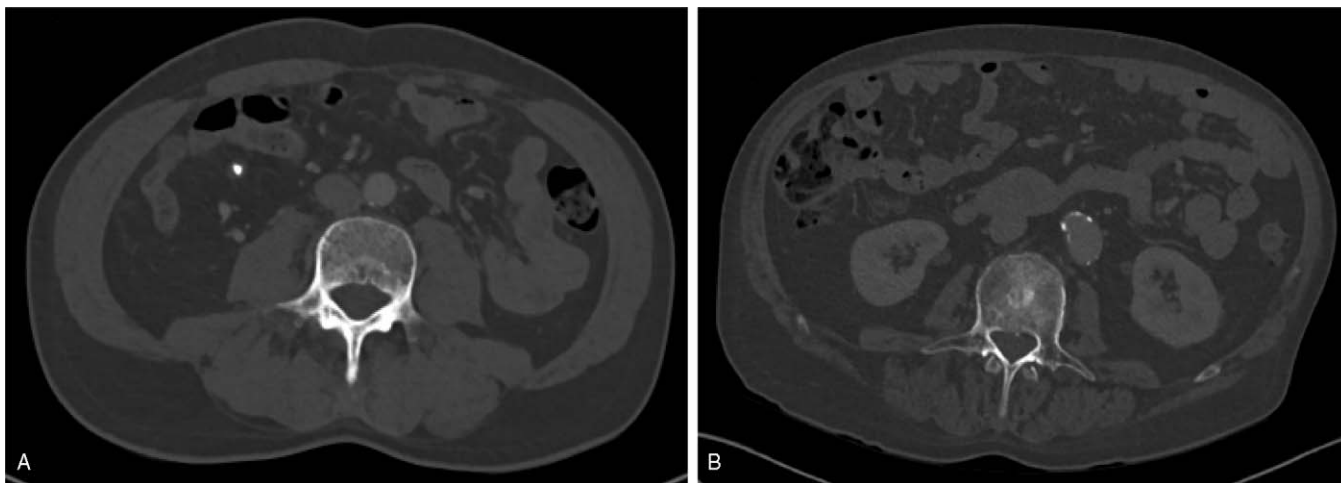
Figure 4. Exemplary Computed Tomography (CT) images of a patient with a large (24.26 cm^2) (A) and a small psoas area (15.43 cm^2) (B) are shown.
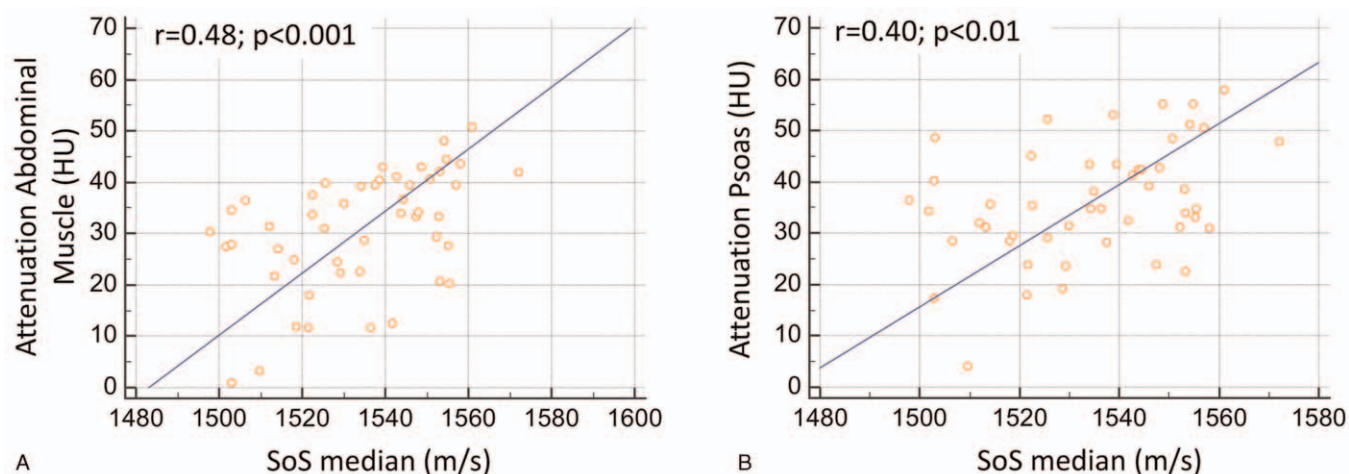

Figure 5. Correlation plots Speed of Sound (SoS) – CT parameter: Correlation plots of SoS and abdominal muscle (a) and psoas muscle (b) attenuation are shown.

sarcopenia diagnosis.[7] 26.4% of patients were characterized as sarcopenic and 73.6% as non-sarcopenic. Receiver operating characteristic analysis revealed an AUC = 0.724 (P = .008), sensitivity = 64.3% and specificity = 85.7%. (Fig. 6). The SoS comparison between sarcopenic and non-sarcopenic patients was not significant based on the threshold values[7,22] of psoas index (P = .2997), SMA (P = .5394), and SMI (P = .5655).

3.3. Inter-examiner agreement for SoS

The median difference between both examiners was −3.4 m/s with ICR = 15.1 m/s and intraclass correlation coefficient = 0.794.

4. Discussion

In the presented study, sonographically assessed SoS of calf tissue correlated moderately with CT abdominal muscle and psoas muscle attenuation at the level of L3. It correlated moderately with abdominal area and weakly with subcutaneous fat area. Abdominal and psoas muscle normalized to abdominal area correlated moderately and weakly with SoS.

It has been shown that psoas muscle area predicts outcomes after aortic aneurysm repair[40] and cardiac surgeries.[41] This parameter has been shown not to be representative of total

Table 1		

Correlation of SoS with CT parameters (significance level P = .05). n.s = not significant.

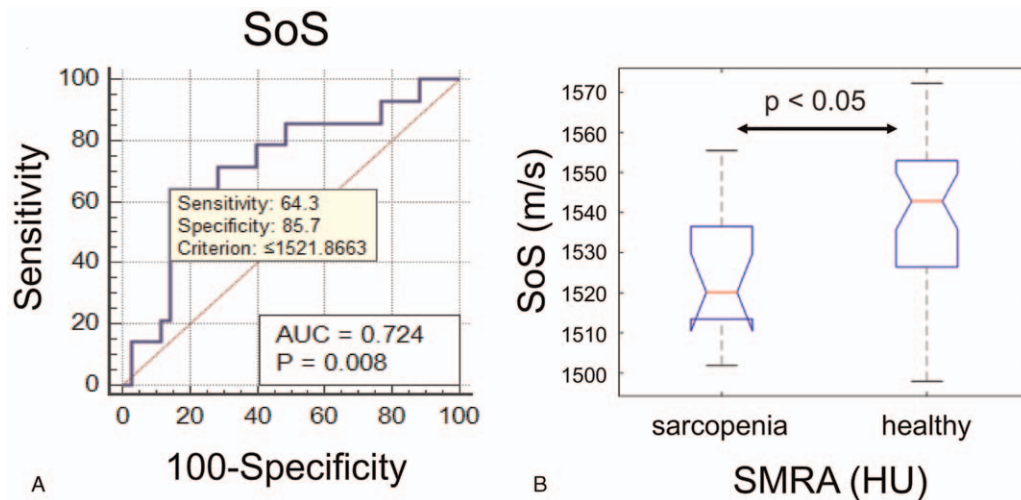| CT		SoS Median
Psoas	Area (cm^2)	n.s.
	Psoas area/Abdominal muscle area	0.39
	Attenuation (HU)	0.40
Abdominal muscle	Area (cm^2)	n.s.
	Abdominal muscle area/Abdominal area	0.43
	Attenuation (HU)	0.48
Abdominal	Area (cm^2)	−0.44
Visceral fat	Area (cm^2)	n.s.
Subcutaneous fat	Area (cm^2)	−0.37

Figure 6. Diagnostic accuracy: Receiver operating characteristic (ROC) curve (A) and boxplots (B) based on skeletal muscle radiation attenuation (SMRA) threshold values[7] for sarcopenia are shown.

skeletal muscle area in patients with ovarian cancer.[42] In our study, SoS correlated significantly with normalized psoas and abdominal muscle area. Therefore, SoS might have potential as a prognostic factor.

We found a moderate, significant correlation of SoS with the attenuation of psoas and abdominal muscle, which is related to physical function.[17,18] This significant correlation could further strengthen the potential of SoS as a surrogate parameter in predicting physical function. In a geriatric context, SoS might have value in the risk assessment of falls and could possibly reduce the number of fall-associated injuries through early preventive measures. In addition, complications of sarcopenia, such as pneumonia,[3] could be prevented through early detection and appropriate measures.

Comparing SoS and the reference standards for fat content estimation of the same body region, very strong to strong correlations were found for muscle[27] and breast.[43] In our study, slices of two different body regions, each acting as surrogate parameters, SoS as a potential surrogate for physical function of the lower extremity with consecutive fall risk assessment and the L3 slice as a surrogate for several clinical outcome parameters, were compared. Reasons for the moderate, non-strong correlations found in this study could lie in the indirect nature of the comparison with different influencing factors of the investigated body regions. Moreover, comparing the physical properties of both techniques, SoS in a medium is based on the medium's bulk modulus (K) and its density (ρ) according to the relationship $c = \sqrt{(K/\rho)}$,[44] whereas the attenuation of x-rays by a certain material depends on the energy of x-ray photons as well as on material thickness, density and atomic number.[45]

It has been shown that BMI does not precisely assess the body fat amount.[4] In this study, SoS was superior compared to BMI in predicting abdominal muscle and psoas muscle attenuation as well as psoas muscle area normalized with abdominal area. Compared to SoS, BMI was a superior predictor of abdominal, visceral and subcutaneous fat areas.

Some studies have acknowledged the capability of ultrasound for muscle loss assessment with parameters such as echogenicity, pennation angle, muscle thickness and muscle strength.[46,47] In

the last years, first protocols have been set up aiming to standardize measurements.

SoS is a quantitative imaging biomarker, which measures the propagation velocity of longitudinal waves in tissues. Recent research works have shown the potential of SoS to differentiate fatty muscular degeneration,[48] adipose breast tissue from glandular tissue,[25] benign from malignant breast lesions[49] and different severity stages of liver steatosis.[26] Currently available commercial SoS imaging systems are three-dimensional ultrasound computed tomography (USCT) devices utilizing a water bath, which are mainly used for imaging of the breast[44] and limb.[48] However, measurements of the extremities are affected by bone, which introduces strong distortions in SoS measurements.[48] Hand-held two-dimensional SoS-US is a novel, low-cost, easy-to-perform technique, which uses conventional ultrasound systems to measure SoS with a reflector add-on as a time reference and without the need of a water bath.[48,50] Based on known SoS differences between muscular (1585 m/s) and adipose (1440 m/s) tissue,[24] significant SoS differences between healthy and sarcopenic individuals[23] as well as strong correlations with MRI fat fraction[27] have been found for the lower leg, which led to a demand for further studies comparing the novel technique with clinical reference standards,[51] as presented by this study.

Limitations of this study include the indirect nature of the comparison, the low number of patients and possible selection bias of the patient population, which is characterized by a history of endovascular aortic repair. Limitations of the L3 muscle area technique include possible influences of scoliosis on the surface area measurements. In addition, the cut-off values are based on CT images from non-enhanced CT phase or CT images without any specification regarding contrast agent application.[7,22] However, it has been shown that the influence of contrast agent application on skeletal muscle radiation attenuation assessed with computed tomography muscle measurements is small, although significant,[52] with very strong correlations between non-contrast and contrast phases.[53,54] The non-standardization with regard to contrast agent application, which has been studied by Amini et al.,[55] as well as the influence of changing kV and slice thickness on skeletal muscle radiation attenuation[52]

present limitations of muscular composition assessment with CT and further strengthen the need for further modalities, such as ultrasound.

Giving an outlook, next steps include the evaluation of the generalizability of calf measurements by comparison with whole-body fat measurements and, as a technical milestone, the investigation of a new SoS technique, which is based on intrinsic tissue reflections serving as an "internal reflector,"[56] for muscle assessment.

In conclusion, there were moderate correlations between SoS and standard CT parameters for muscle loss assessment, despite the indirect nature of comparison. SoS measurements of the calf were moderately accurate based on CT sarcopenia threshold values. Therefore, SoS shows potential as a surrogate parameter for a radiation-free, inexpensive muscle loss quantification using a standard ultrasound machine.

Acknowledgments

Author contributions

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