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The current use of ultrasound to measure skeletal muscle and its ability to predict clinical outcomes: a systematic review

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Abstract

Quantification and monitoring of lean body mass is an important component of nutrition assessment to determine nutrition status and muscle loss. The negative impact of reduced muscle mass and muscle function is increasingly evident across acute and chronic disease states but is particularly pronounced in patients with cancer. Ultrasound is emerging as a promising tool to directly measure skeletal muscle mass and quality. Unlike other ionizing imaging techniques, ultrasound can be used repeatedly at the bedside and may compliment nutritional risk assessment. This review aims to describe the current use of skeletal muscle ultrasound (SMUS) to measure muscle mass and quality in patients with acute and chronic clinical conditions and its ability to predict functional capacity, severity of malnutrition, hospital admission, and survival. Databases were searched from their inception to August 2021 for full-text articles in English. Relevant articles were included if SMUS was investigated in acute or chronic clinical contexts and correlated with a defined clinical outcome measure. Data were synthesized for narrative review due to heterogeneity between studies. This review analysed 37 studies (3100 patients), which met the inclusion criteria. Most studies (n = 22) were conducted in critical care. The clinical outcomes investigated included functional status at discharge (intensive care unit-acquired weakness), nutritional status, and length of stay. SMUS was also utilized in chronic conditions such as chronic obstructive pulmonary disease, chronic heart failure, and chronic renal failure to predict hospital readmission and disease severity. Only two studies investigated the use of SMUS in patients with cancer. Of the 37 studies, 28 (76%) found that SMUS (cross-sectional area, muscle thickness, and echointensity) showed significant associations with functional capacity, length of stay, readmission, and survival. There was significant heterogeneity in terms of ultrasound technique and outcome measurement across the included studies. This review highlights that SMUS continues to gain momentum as a potential tool for skeletal muscle assessment and predicting clinically important outcomes. Further work is required to standardize the technique in nutritionally vulnerable patients, such as those with cancer, before SMUS can be widely adopted as a bedside prognostic tool.

Keywords Skeletal muscle; Ultrasound; Muscle wasting; Sarcopenia; Malnutrition; Risk prediction

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Background

Assessment of body composition goes beyond measuring overall body weight and is an important component of nutritional assessment in patients with both acute and chronic illness. European and American Societies for Parenteral and Enteral Nutrition guidelines (ESPEN, ASPEN) recommend the routine assessment of body composition with specific emphasis on lean mass.[1,2] Skeletal muscle is the major component of lean body mass and plays an important homeostatic, metabolic, and physical functioning role. There is now a wealth of data to show that patients with reduced muscle mass and function (sarcopenia), and those who suffer acute muscle wasting during treatment, are at higher risk of treatment-related complications, take longer to recover, and have worse overall survival.[3–7] This phenomenon transcends disease types but is especially pronounced in patients who are nutritionally vulnerable such as older patients and those with cancer.[8] Low muscle mass combined with obesity is a particularly dangerous combination where significant loss of muscle may go undetected by simply monitoring body weight or anthropometrics alone.[9] An appropriate bedside test is therefore required to quantify both muscle mass and quality so longitudinal changes in muscle can be monitored to help inform decisions about treatment and nutritional support. Whilst several tools exist for this purpose, each have their own technical pitfalls and practical limitations. Computer tomography (CT) and magnetic resonance imaging (MRI) are excellent at quantifying muscle mass and, more recently, muscle quality (myosteatosis).[5] Whilst cross-sectional imaging can be retrospectively analysed, requesting these investigations for the sole intention of body composition analysis is not appropriate due to practical constraints, expense, and (in the case of CT) ionizing radiation. The ideal test should be inexpensive, non-ionizing, accurate, and sensitive enough to detect even small changes in muscle mass or quality. Ultrasound is emerging as a promising bedside tool for this purpose. Originally used to describe changes in adipose tissue (subcutaneous and visceral fat thickness),[10] the focus has moved to the assessment skeletal muscle. The European Working Group on Sarcopenia identify ultrasound as a potentially useful method for evaluating skeletal muscle whilst accepting that further research is required.[11] Muscle thickness, cross-sectional area (CSA), echointensity, pennation angle, and fascicle length are the key variables that offer both quantitative and qualitative analyses of muscle tissue. The validity and reliability of ultrasound to measure skeletal muscle has been the subject of recent systematic review and shown to have good interclass correlation coefficient and validity when compared with other imaging modalities.[12–14] When standardized for age and sex, a four-site protocol (bilateral quadriceps and biceps) demonstrates excellent agreement with reference standards such as dual x-ray absoripitometry (DEXA) (R^2 = 0.91).[15] Initial concerns regarding the lack of a standardized ultrasound technique are beginning to be answered as evidence from the geriatric and critical care setting expands.[16–18] Furthermore, recent consensus guidelines on the optimal technique for each muscle site have been published and offer well-evidenced practical advice to further improve the reproducibility and validity of skeletal muscle ultrasound (SMUS).[19] With this foundation, attention is now turning to the power of muscle ultrasound to inform and predict clinical and health-related outcomes. Before SMUS can become a reliable and integrated nutritional assessment tool, its ability to predict patient-centred outcomes requires investigation. The aim of this systematic review is to describe the current use of SMUS measurements (CSA, muscle thickness, and echogenicity) and its ability to predict clinically relevant outcome measures, such as functional capacity, length of stay, readmission, and survival in acute and chronic clinical contexts.

Search methods

PubMed, Cochrane Library, Embase, Ovid, Scopus, and Google Scholar were systematically searched for full-text articles in English from inception up until 1 August 2021. Outcomes of interest included the use of SMUS of any anatomical location (other than the diaphragm), which were associated with a clinical or functionally relevant outcome. The search included a combination of terms related to muscle mass, nutritional assessment, ultrasound, and clinical outcomes. Included was a combination of terms related to muscle mass, nutritional assessment, ultrasound, and clinical outcomes were used: (i) sarcopenia: muscular atroph*, muscle atroph*, muscle mass*, muscle size*, muscle diameter*, muscle volume*, muscle thickness*, muscle wasting; (ii) ultrasonography: ultrasound, ultraso* imaging, sonography; and (iii) nutrition*, nutrition screening, malnutrition. In addition, published reference lists were hand-searched and screened for additional resources.

Study eligibility and appraisal criteria

A broad range of disease types and clinical contexts were considered with the exception of papers assessing systemic neuromuscular pathology (e.g. hemiplegic stroke and neuromuscular degeneration) or primary muscular pathology (e.g. myositis), which were excluded. Studies were only included if reference to a specific and defined clinical or functional outcome was made as part of their primary analysis. These included acute admission metrics (complications, length of stay, length of ventilation, readmission, and in-hospital mortality), any validated assessment of functional, nutritional, and quality of life status, or survival. Studies that compared or validated ultrasound metrics to other modalities (e.g. bioelectrical impedance analysis, CT, and MRI) or studies that only addressed technical aspects of ultrasound technique were excluded as this has been subject of recent systematic review.[19] Studies in children (<18 years old) were also excluded.

Search results were exported, and duplicates deleted using Mendeley Desktop (2020, Version 1.19.8). After title and abstract screening, full-text articles were assessed for eligibility and quality and independently reviewed by two assessors (P. C. and M. A.). Disagreements were resolved by review and consensus by the senior lead author (J. S.). Studies were independently scored to assess methodological quality and relevance according to COSMIN guidelines plus a modified 10-point checklist modified from Pretorius and Keating who validated real-time ultrasound measurements of skeletal muscle.[20] The consensus-based standards for the selection of health status measurement instruments (COSMIN) checklist consists of nine boxes containing multiple criteria, which are used to assess methodological quality. A score was determined by taking the lowest rating of each criterion and defined to be poor, fair, good, or excellent.[21] Methodological quality was scored independently between reviewers, and agreement assessed using Cohen's kappa coefficient where a score of >0.75 suggested excellent agreement, 0.75–0.4 as fair to good, and <0.4 as poor agreement between reviewers.[22] Data were extracted from full manuscripts and imported for analysis. Data points collected included the clinical context of the study, technical aspects of the ultrasound equipment, scan technique adopted, the clinically relevant outcome investigated, and the statistical analysis used to assess correlations. Observational and cohort studies were classified as 'positive' if a statistically significant correlation (i.e. P value < 0.05) was reported using appropriate statistical methodology. Negative studies were those that found no statistically significant association. Those lacking statistical or methodological detail (i.e. poor on COSMIN scoring and <6 on the modified quality checklist) were excluded from the review analysis. Randomized control trials were assessed using the same criteria; that is, ultrasound measures correlation with a defined clinical outcome even if this was measured as a secondary outcome. Preliminary assessment of the combined data demonstrated significant heterogeneity in terms of clinical context and outcome measures; therefore, no met-analysis was performed.

Results

A summary of the study search process is outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram (*Figure* 1). After screening by title and abstract, 53 studies were assessed[23] in detail for eligibility. A total of 37 studies (involving 3100 participants) were deemed eligible based on quality and relevance. The inter-rater agreement regarding study eligibility was rated excellent [Cohen's kappa = 0.79 (95% confidence interval = 0.67 to 0.92)], and the agreement on the above defined methodological quality of each study was rated good [Cohen's kappa = 0.61 (95% confidence interval = 0.51 to 0.71)]. The number of publications over the last 18 months (n = 18 studies) was similar to that of the preceding 11 years (n = 19 studies) highlighting the recent surge of new evidence (*Figure* 2). Data from 26 prospective observational studies[23–43] (of which 6 were cohort studies,[44–49] 7 cross-sectional

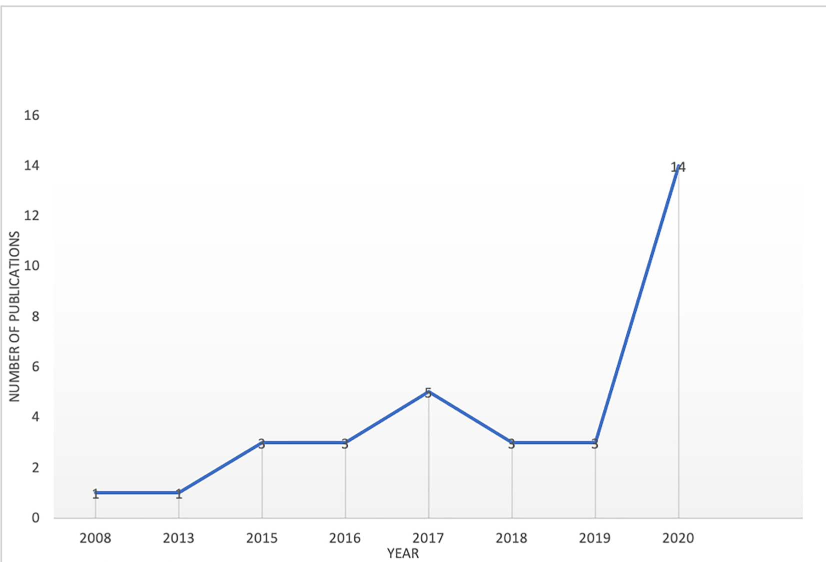

Figure 1 Graph of publications over time pertaining to skeletal muscle ultrasound as a clinical prediction tool.

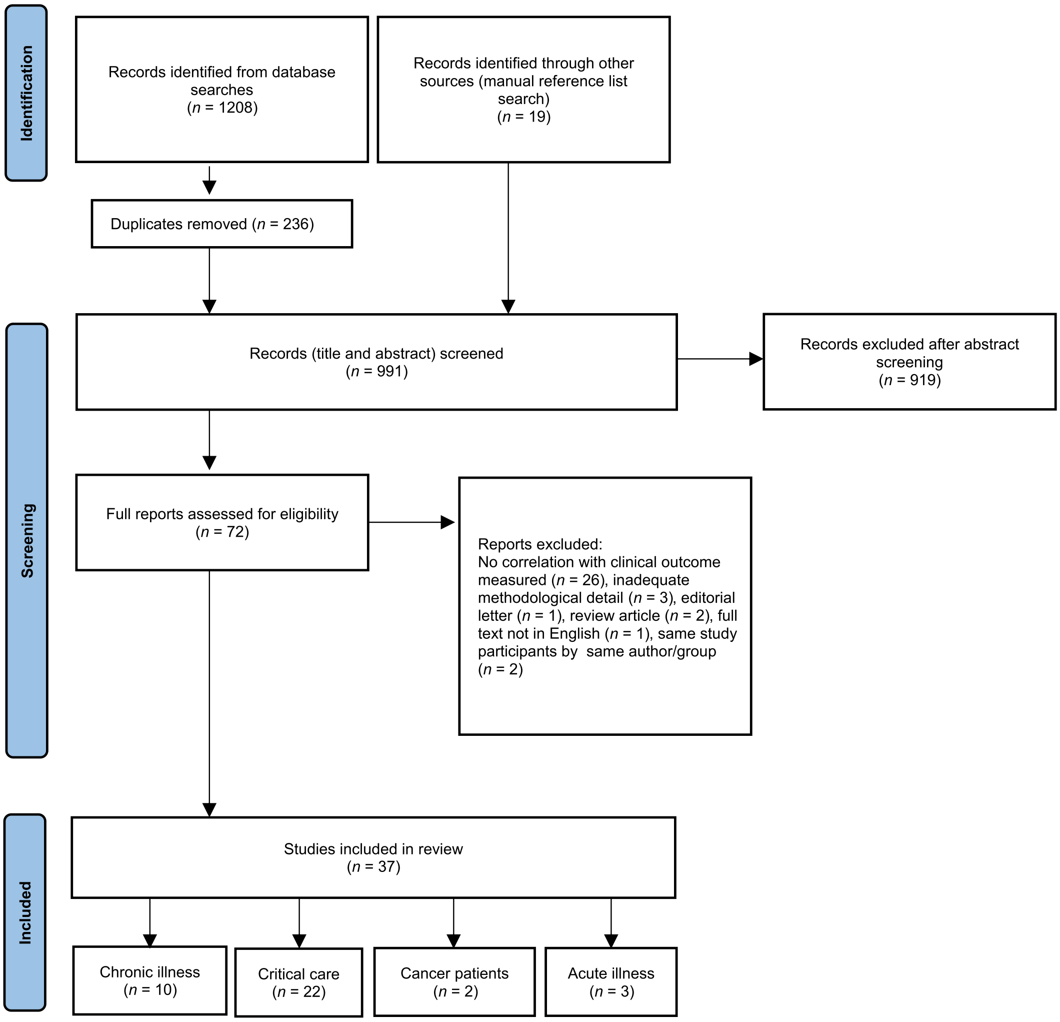

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing selection procedure.

studies,[27,50–55] 3 randomized control trials,[56–58] and 1 post hoc analysis of a negative trial) were included.[59] Five of the 37 studies involved an interventional arm [critical care nutritional intervention (*n* = 4)[44,56–58] and an exercise intervention in breast cancer (*n* = 1)[45]].

Clinical context

Most studies (59%) were conducted in the critical care unit and described the impact of ultrasound-derived muscle loss in a general critical care population as part of their study. Ten studies (27%) investigated patients with chronic disease in the outpatients setting [chronic obstructive pulmonary disease (COPD) *n* = 4,[26,34,52,55] heart failure *n* = 2,[51,53] chronic renal failure *n* = 2,[27,54] geriatric rehabilitation *n* = 1,[23] and liver cirrhosis *n* = 1[31]] whereas three studies were conducted during an acute admission (acute surgical,[40] exacerbation of COPD,[59] and acute geriatric admission[46]). Only two studies were conducted in patients receiving treatment for cancer.[45,50] Of the 37 studies, 15 reported the specialty and expertise of the individual performing the scans, dieticians (*n* = 6) and medical staff (*n* = 6) being the most frequently reported ultrasound technicians.

Correlation with outcomes

Overall, 28 of the 37 studies (76%) were classified as a positive study having reported a statistically significant association between SMUS and a defined clinical or functional outcome. Two of the remaining nine negative studies reported strong trends on univariate analysis, which were then lost on multivariate analysis.[40,46] The remaining seven negative studies found no association or correlation with any of the outcomes investigated. The mean number of patients recruited in the negative studies was 56 (±29), compared 91 (±63) in the positive studies (*P* = 0.049). *Table* 1 summarizes

Table 1 Summary of studies included

First author	Year	Clinical context	*n* =	Muscle group	Technique described	US metric
Akazawa[23]	2021	Subacute - geriatric rehab	404	RF, VI	1/3 thigh, no pressure	MT, EI
Bloch[24]	2013	ITU - cardiothoracic surgery	42	RF	Mid-thigh, no pressure	CSA
Bury[44]	2020	ITU - surgical	52	RF, VI	1/3 and 1/2 thigh, max pressure	MT
Chapple[25]	2016	ITU - head injury	37	RF, VI	1/3 and 1/2 thigh, max pressure	MT
Cruz-Montecinos[26]	2016	Chronic - COPD rehab	20	RF, VI	1/3 thigh, no pressure	MT, EI
de Souza[27]	2018	Chronic - CKD pre-dialysis	100	RF	Mid-thigh, no pressure	CSA
Dimopoulos[28]	2020	ITU - cardiac surgery	165	RF, VI	Mid-thigh, no pressure	MT
Escriche-Escuder[45]	2021	Cancer - breast cancer	13	RF, VI, BB	Yes - but different to most other studies	MT, EI
Ferrie[56]	2015	ITU - general	119	RF, VI, BB, forearm	1/3 and 1/2 thigh, no pressure	MT, CSA
Fetterplace[57]	2018	ITU - general	60	RF, VI	1/3 and 1/2 thigh, no pressure	MT
Galindo Martín[29]	2017	ITU - general	59	RF, VI	Mid-thigh, max pressure	MT
Gomes[50]	2020	Cancer complications/treatment	41	RF, VI	Inadequate detail	MT
Greening[59]	2015	Acute - COPD	191	RF	Mid-thigh, no pressure	CSA
Gruther[30]	2008	ITU - general	118	RF, VI	1/3 thigh, no pressure	MT
Guerreiro[46]	2017	Acute - geriatric	100	RF, VI	Mid-thigh, no pressure	MT, total Th, contract index
Hari[31]	2019	Chronic - cirrhosis	54	Psoas	Internal SOP	PMI PtHR
Hayes[47]	2018	ITU - ECMO	25	RF, VI, VL	1/3 thigh, no pressure	MT, EI, CSA
Lee[32]	2020	ITU - general	86	RF, VI	1/3 thigh, no pressure	MT, CSA, EI, PA, FL
Mayer[33]	2020	ITU - general	41	RF, TA	1/3 thigh, no pressure	MT, CSA, EI
Maynard-Paquette[34]	2020	Chronic - COPD	40	RF, VI	3/5 thigh, no pressure	MT, CSA, Q contractile index
McNelly[58]	2020	ITU - general	121	RF	3/5 thigh, no pressure	CSA
Mueller[48]	2016	ITU - surgical	102	RF	60% point, no pressure	CSA
Nakano[51]	2020	Chronic - HF	58	RF, VI, VM, VL	Mid-thigh, no pressure	MT, EI
Nijholt[52]	2019	Chronic - COPD rehab	30	RF	Mid-thigh, no pressure	MT, CSA
Palakshappa[35]	2018	ITU - sepsis	18	RF, VI	1/3 thigh, no pressure	MT, CSA
Parry[26]	2015	ITU - general	22	RF, VI, VM, VL	1/3 thigh, no pressure	MT, CSA, EI, PA
Pita[27]	2020	ITU - liver failure	50	RF	3/4 mark, no pressure	CSA (normalized to body SA)
Puthucheary[28]	2017	ITU - general	54	RF, VI	Mid-thigh, no pressure	MT, CSA
Rodrigues[29]	2020	ITU - general	60	RF, VI	1/2 and 1/3 thigh, no pressure	MT, CSA
Sabatino[30]	2021	ITU - renal	30	RF, VI	Mid-thigh, no pressure	MT
Salim[31]	2020	Acute - surgical	49	RF, VI	Mid-thigh, max pressure	MT (normalized for limb length)
Sato[32]	2020	Chronic - HF	185	RF	Mid-thigh, no pressure	MT
Sahatheven[33]	2020	Chronic - CKD on dialysis	351	RF	1/3 thigh, no pressure	CSA
Tanaka[34]	2020	ITU - sepsis	8	RF	Mid-thigh, no pressure	MT
Toledo[35]	2021	ITU - general	74	RF, VI	1/3 and 1/2 thigh, no pressure	MT
Witteveen[36]	2017	ITU - general	71	RF, TA, BB, FCR	Yes - defined landmarks for each muscle group	MT, EI
Ye[37]	2017	Chronic - COPD	50	RF, VI	Mid-thigh, no pressure	MT, CSA, EI

6MWT, 6 min walk test; ADL, activities of daily living; ASPEN, American Society of Parental and Enteral Nutrition; BB, biceps brachii; CFS, clinical frailty score; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; CSA, cross-sectional area; D/C, discharge; ECMO, extra-corporeal membrane oxygenation; EI, echointensity; FCR, flexor carpi radialis; FEV1, forced expiratory volume 1; FFM, fat free mass; FL, fascicle length; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GOS-E, Global Outcome Scale - Extended; HGS, hand grip strength; ICU, intensive care unit; ISRNM, International Society of Renal Nutrition and Metabolism; ISWT, intermittent shuttle walk test; ITU, intensive treatment unit; ITU-AW, intensive treatment unit-acquired weakness; LBM, lean body mass; LOCCS, length of critical care stay; LOMV, length of mechanical ventilation; LOS, length of stay; MRC, medical research council strength score; MT, muscle thickness; MVCQ, mean voluntary contraction index; NUTRIC, nutritional risk in critically ill; PA, pennation angle; PEW, protein energy wasting; PG-SGA, Patient-Generated Subjective Global Assessment; PMI, psoas muscle index; PtHR, psoas to height ration; QLQ-BR, Quality of Life Questionnaire - Breast Cancer; QoL, quality of life; RF, rectus femoris; SA, surface area; SARC-F, strength, assistance, rising, climbing, and falls score; SF-36, short form-36; SOFA, Sequential Organ Failure Assessment; SOP, standard operating procedure; StS, sit to stand; TA, tibialis anterior; US, ultrasound; VI, vastus intermedius.

Table 1 (continued)

First author	Serial measurements	Clinical outcome investigated	Intervention	Main conclusion	Positive or negative study
Akazawa[23]	N	Barthel Index (ADL)	N	Poor echointensity on US correlates with delayed recovery of ADL	Positive study
Bloch[24]	Y - D0 and D7	LOS, mortality, circulating biomarkers	N	No correlation with clinical outcomes. Phenotypes of wasters vs. non-wasters identified	Negative study
Bury[44]	Y - D0–10	ASPEN nutrition grade, LOS, vent days	Y - nutrition supplement	US can detect muscle loss and correlates with degree of malnutrition	Positive study
Chapple[25]	Y - weekly and 3/12 post-discharge	Physical function (SF-36), GOS-E	N	US detects muscle loss and correlates with physical functioning role and LBM	Positive study
Cruz-Montecinos[26]	N	6MWT, MVCQ	N	US correlates with exercise capacity and strength	Positive study
de Souza[27]	N	HGS, gait speed	N	US correlates with HGS	Positive study
Dimopoulos[28]	Y - D1, 3, 5, 7	MRC score, LOCCS, LOMV	N	Baseline low MT is associated with prolonged ITU stay	Positive study
Escriche-Escuder[45]	Y - Week 0 and Week 12	QLQ-BR 23	Y - 12 week mixed exercise	Exercise intervention improved MT and EI. Upper limb MT correlated with improved QoL ($r = 0.61$)	Positive study
Ferrie[56]	Y - D0, 3, 7	LOS, mortality, fatigue scores on univariate analysis only	Y - nutrition supplement	Extra nutritional supplement improves MT and fatigue scores	Positive study
Fetterplace[57]	Y - D0 and D15	HGS, malnutrition (PG SGA), MRC score	Y - nutrition supplement	Intervention attenuated loss of muscle thickness. No correlation with outcomes measured	Negative study
Galindo Martín[29]	N	Mortality, NUTRIC status	N	MT was greater in the group that survived (1.4 cm vs. 0.98 cm) and independent of disease severity (SOFA)	Positive study
Gomes[50]	N	SARC-F - sarcopenia risk	N	US measure of MT correlates with SARC-F score	Positive study
Greening[59]	N	Readmission, death, LOS	N	Small RF CSA associated with increased risk of death and readmission and LOS	Positive study
Gruther[30]	Y - 17 patients. Sporadic measures	LOS	N	US measure of MT correlates with LOS on ITU	Positive study
Guerreiro[46]	N	Functional decline, death, readmission at 3 months	N	US of MT may predict functional decline, rehospitalization, and death	Positive signals
Hari[31]	N	Readmission and death	N	A low psoas muscle index on US predicted risk of hospitalization and death	Positive study
Hayes[47]	Y - D0, 10, and 20	MRC score, HGS, ICU mobility scale	N	US can detect muscle loss and EI correlated with strength and mobility scores	Positive study
Lee[32]	Y - D1, D7, D14 and at D/C	60 day mortality, mNUTRIC, SARCF, CFS, ADL	N	1% reduction in MT on ITU = 5% increase in 60 day mortality	Positive study
Mayer[33]	Y - D1 and D7	ITU-acquired weakness, StS	N	EI change during first 7 days correlated with physical function (ITU-AW) at discharge	Positive study
Maynard-Paquette[34]	N	Acute admissions, disease severity using symptom tool and FEV1	N	US quadriceps contractile index correlates with disease symptoms and severity	Positive study
McNelly[58]	Y - D1, 7, and 10	Functional (sit to stand)	Y - intermittent vs. Cont feed	No impact from intervention. SMUS not associated with functional status	Negative study

Table 1 (continued)

First author	Serial measurements	Clinical outcome investigated	Intervention	Main conclusion	Positive or negative study
Mueller[48]	N	Discharge destination, frailty index	N	Muscle US predicts discharge destination in acute surgical patients	Positive study
Nakano[51]	N	Exercise tolerance (CPET variables)	N	Increased EI of thigh muscle is associated with worse exercise tolerance (based on peak VO_2)	Positive study
Nijholt[52]	N	HGS, StS, ISWT	N	US correlates modestly with total FFM and HGS	Negative study
Palakshappa[35]	Y - D0 and D7	MRC score and physical function in ITU (PFIT-s)	N	Only modest correlation with functional strength at Day 7	Negative study
Parry[26]	Y - D1, 3, 5, 7, 10, and D/C	ITU-acquired weakness	N	MT and EI correlated with functional status at discharge	Positive study
Pita[27]	Y - every 2 days	Survival	N	RF CSA is associated with worse survival	Positive study
Puthucheary[28]	Y - D1 and D7	Muscle strength (MRC score)	N	Changes in RF CSA during critical illness predicted functional weakness	Positive study
Rodrigues[29]	Y - every 2 days	Nutrition status (GLIM, PG-SGA), LOS, LOMV, death	N	No correlation with outcomes measured	Negative study
Sabatino[30]	Y - D0 and D5	Discharge destination	N	Severe muscle loss on US predicted LOS and discharge destination. OR 0.04 (0–0.74)	Positive study
Salim[31]	N	Post-op complications and frailty	N	US thigh identifies frail patients. Non-significant trend towards complication rates	Negative study—non-significant trend only
Sato[32]	N	Fitness (on CPET) and functional capacity	N	RF MT correlates well with exercise tolerance and physical fitness	Positive study
Sahatheven[33]	N	Nutrition status as per ISRNM criteria for PEW	N	US measures of RF CSA correlate with malnutrition and outperform indirect methods	Positive study
Tanaka[34]	Y - alternate days	Physical function as per Barthel ADL index, LOCCS	N	Change in RF thickness is associated with LOS and functional capacity after 30 days	Positive study
Toledo[35]	Y - alternate days	Survival, need for MV	N	Decrease in MT was associated with longer need for mechanical ventilation	Positive study
Witteveen[36]	N	ITU-acquired weakness (MRC score < 4)	N	Ultrasound does not predict ICU-AW	Negative study
Ye[37]	N	HRQoL, functional assessment, disease severity (GOLD)	N	EI on US is associated with QoL, physical functioning, and disease severity	Positive study

6MWT, 6 min walk test; ADL, activities of daily living; ASPEN, American Society of Parental and Enteral Nutrition; BB, biceps brachii; CFS, clinical frailty score; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; CSA, cross-sectional area; D/C, discharge; ECMO, extra-corporeal membrane oxygenation; EI, echointensity; FCR, flexor carpi radialis; FEV1, forced expiratory volume 1; FFM, fat free mass; FL, fascicle length; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GOS-E, Global Outcome Scale - Extended; HGS, hand grip strength; ICU, intensive care unit; ISRNM, International Society of Renal Nutrition and Metabolism; ISWT, intermittent shuttle walk test; ITU, intensive treatment unit; ITU-AW, intensive treatment unit-acquired weakness; LBM, lean body mass; LOCCS, length of critical care stay; LOMV, length of mechanical ventilation; LOS, length of stay; MRC, medical research council strength score; MT, muscle thickness; MVCQ, mean voluntary contraction index; NUTRIC, nutritional risk in critically ill; PA, pennation angle; PEW, protein energy wasting; PG-SGA, Patient-Generated Subjective Global Assessment; PMI, psoas muscle index; PtHR, psoas to height ration; QLQ-BR, Quality of Life Questionnaire - Breast Cancer; QoL, quality of life; RF, rectus femoris; SA, surface area; SARC-F, strength, assistance, rising, climbing, and falls score; SF-36, short form-36; SOFA, Sequential Organ Failure Assessment; SOP, standard operating procedure; StS, sit to stand; TA, tibialis anterior; US, ultrasound; VI, vastus intermedius.

the variety and frequency of different outcomes investigated. Outcomes investigated were categorized into survival, length of stay, hospital (re)admission, functional capacity (including intensive care unit-acquired weakness), physical fitness, nutritional risk status, quality of life, discharge destination, and need for mechanical ventilation.

Cross-sectional area of rectus femoris (RF) and muscle thickness of the quadriceps [combining RF and vastus intermedius (VI) thickness] were the most frequently measured metrics used to correlate against a clinical or functional outcome measure. Of the 10 studies that investigated echointensity of quadriceps (indicating muscle quality/fat content), 7 found statistically significant correlations with clinical and functional outcomes.[23,26,32,33,36,43,45,47,51,55] Twenty studies took serial measurements of the same muscle group to describe longitudinal changes in muscle mass. All 20 of these longitudinal studies found statistically significant changes in muscle measurements over time, which ranged from 15% to 30% reduction in muscle measurement between Day 0 (baseline) and Day 20.[24,25,28,30,32,33,35–39,41,42,44,45,47,49,56–58]

Ultrasound technique and protocol

Adequate detail regarding the equipment used and scan technique was reported in 86% of the studies. These studies described a clear and reproducible protocol regarding anatomical landmarks, ultrasound settings, and image analysis methods. The remaining 14% lacked enough detail to allow reproducibility of scan technique. Despite this, these studies remained in the review analysis due to their relevance and otherwise good methodological quality (checklist score > 6). Bright mode (B-mode) ultrasound with frequencies between 3 and 15 MHz was used by all the reporting studies. Linear transducers were used in most of the studies (94%), and curved array transducers used in remaining 6%. Only half of the studies (54%) reported inter-rater and intra-rater reliability to determine agreement between scans. In these studies, intraclass correlation coefficients ranged from 0.82 to 0.99 indicating good reliability and reproducibility of the technique used.

Quadriceps femoris (RF, VI, lateralis, or medialis) was the most frequently scanned muscle group and investigated in all but one of the included studies. Other groups included biceps brachii, tibialis anterior, flexor carpi radialis, and psoas. Four of the studies included both upper and lower limb measurements.[33,43,45,56] The most frequently adopted anatomical landmarks were the midpoint of the thigh between anterior superior iliac spine and the superior border of patella (38%), the distal point measured at 2/3rd distance (24%), or both (16%). Other novel measurement landmarks were the distal 75% and 60% point of the thigh (n = 4), justified by the point at which the whole of RF could be included in the image. Only four of the studies used maximum probe compression technique with minimum probe compression being used in the majority.[25,29,40,44]

Ultrasound metrics measured included muscle thickness, CSA, echointensity, fascicle length, and pennation angle. Half of the studies measured a single metric only. Muscle thickness and/or CSA was the most frequently used metric measured in 29 of the 37 studies. CSA was measured on its own in seven studies. Echointensity was assessed in only 10 of the studies with fascicle length and pennation angle being rarely measured, appearing in only 2 of the studies. Three of the studies adjusted ultrasound measurements to either the patients' height, limb length, or body surface area to produce a novel indexed value.[31,40,49]

The highest-ranking studies based on the highest methodological quality on the COSMIN and modified 10-point checklist are summarized in *Table* 2.[23,28,48,53,59]

Discussion

The main findings from this review indicate that SMUS can be used successfully to detect changes in both muscle mass and quality across a range on clinical contexts. Most studies (76%) described a statistically significant association between ultrasound measurements and a clinical, functional, or nutritional outcome measure. It is worth noting that 26/37 of the studies included in this review had $<$80 patients in their primary analysis. Several of the studies were underpowered and are at risk of type 1 error, which might overestimate the ability of ultrasound to predict outcomes.

The validity and reliability of SMUS has been subject of recent systematic review and shown to correlate well with other reference measures of muscle mass, even in clinical populations.[12] It is noteworthy that just over half of the studies in this review reported inter-rater and intra-rater reliability to determine agreement between scans. In other words, nearly half of the studies did not report an attempt to internally validate their scan measurements, which may undermine their results. There were common themes reported in terms of ultrasound technique with most studies using either the midpoint of the thigh or the 2/3rd landmark. Despite this, significant heterogeneity still existed with 9 different ultrasound techniques described across the 37 studies. This variation in technique, again, may weaken the conclusions made from this review. Recent work by the Sarcopenia Ultrasound Group (SARCUS) has attempted to offer a standardized technique to measure muscle parameters by consolidating all the known literature and offering consensus expert guidelines.[19] The importance of developing a validated and standardized approach therefore remains imperative to the strength of future research.

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Table 2 Summary and key findings of the five studies with the highest methodology quality score

First author	Quality indicator score	Clinical context	$n =$	Study design	Muscle group	US metric	Serial measure	Outcome investigated	Main findings	Conclusion
Akazawa[23]	9	Subacute - geriatric rehab	404	P-Ob	RF, VI	MT, EI	N	Functional capacity measured by Barthel Index of ADL	EI correlates with BI score at discharge ($\beta = -0.13$, $P < 0.01$) and BI score change during admission ($\beta = -0.23$, $P < 0.01$). No correlation was seen with muscle thickness.	Intramuscular fat infiltration, detected by ultrasound echointensity, correlates with worse recovery of ADLs in older patients
Greening[59]	8	Acute - COPD	191	Subgroup analysis of RCT	RF	CSA	N	Survival, readmission, LOS	Patients with smaller RF CSA were more likely to be readmitted or die within 12 months (odds ratio 0.46, 95% CI 0.22–0.95; $P = 0.035$) and had longer LOS (28.1 vs. 12.2 days, $P = 0.007$).	Ultrasound measure of RF CSA predicted readmission, survival, and LOS
Mueller[48]	9	ITU - surgical	102	P-ObCo	RF	CSA (sex adjusted)	N	Discharge destination, LOS	Low muscle mass on US independently associated with adverse discharge destination (OR 7.49, CI 1.4–38.2) and overall LOS.	Ultrasound measure of sex-adjusted RF CSA predicted adverse discharge disposition following acute surgical admission
Sato[53]	9	Chronic - HF	185	CS	RF	MT	N	Physical fitness (CPET), nutrition risk (geriatric nutrition risk index)	MT correlated with VO2peak ($\beta = 0.326$, $P = 0.002$), disease severity (NYHA class), and nutritional risk score ($r = 0.539$, $P < 0.001$).	Ultrasound measure of muscle thickness correlated with exercise tolerance and other health-related outcomes in patients with heart failure
Dimopoulos[28]	9	ITU - cardiac surgery	165	P-Ob	RF, VI	MT	Y - D1, 3, 5, 7	Length of ICU stay and mechanical ventilation	Low baseline MT (<2.52 cm) was associated with longer ICU stay and longer need for mechanical ventilation.	Baseline low muscle mass on ultrasound can predict adverse ICU outcomes

ADL, activities of daily living; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; CSA, cross-sectional area; EI, echointensity; HF, heart failure; ICU, intensive care unit; ITU, intensive treatment unit; LOS, length of stay; MT, muscle thickness; NYHA, New York Heart Association; OR, odds ratio; RCT, randomized control trial; RF, rectus femoris; US, ultrasound; VI, vastus intermedius.

Although more convenient and practical than CT, MRI, or DEXA, ultrasound still has limitations in certain clinical populations. Most of the studies in this review excluded some patients from their analysis due to poor image quality. Non-diagnostic images are often encountered in patients with significant peripheral oedema, such as those on intensive care or with renal failure. Patients with significant obesity are also challenging to capture quality images for accurate assessment. This suggests that whilst SMUS is widely applicable, it is not universally achievable across all patients. Indeed, data from the studies that reported on image quality showed that approximately 8% of eligible patients were excluded due to unmeasurable ultrasound images. Advanced techniques such as panoramic image capture or low-frequency curved array transducers may overcome these issues, but these techniques are less well validated and require more specialist training.

It is well established that increasing frailty, multiple comorbidities, and advancing age are all associated with declines in muscle mass and function. Whilst many studies attempted to independently correct for this in their statistical analysis, it remains possible that low muscle mass on ultrasound (or muscle loss during a disease course) is simply a surrogate marker for these confounders, which have an established association with worse clinical outcomes.

The quadriceps was the most commonly studied muscle group due to its accessibility and size. However, there are only limited data on predictive equations to estimate whole body muscle mass based on limb measurements alone. It is therefore conceivable that appendicular measures of muscle (or changes over time) do not necessarily reflect whole body muscle mass. Further longitudinal investigation of appendicular muscle atrophy measured by ultrasound and its relationship to whole body muscle atrophy is therefore required.

Most studies were conducted during acute illness with the majority being based on the intensive care unit. Significant muscle atrophy over short periods have repeatedly been shown in this clinical context due to immobilization, nutritional deficits, and the catabolic effects of critical illness. This review highlights the paucity of data available from more chronic conditions and the very limited data from other vulnerable groups such as those with cancer. Baseline sarcopenia, or acute muscle wasting during cancer treatment, is associated with increased treatment complications, reduced quality of life, and reduced survival.[60,61] Further research in high-risk patients with cancer is recommended to investigate if SMUS can complement, or even outperform, current nutritional assessment and help identify patients that need more intensive support through treatment.

The radiological assessment of muscle quality is gaining increasing attention as a potentially more important radiological metric than simple mass measurement. Early evidence suggests that muscle quality may deteriorate before muscle mass and is independently associated with physical fitness, function, and survival.[62-64] Myosteatosis (fat infiltration of muscle) is measured by radiodensity on CT scan and echogenicity (also known as echointensity) using grayscale analysis on ultrasound. Only, 10 of the studies in this review measured echointensity, with 7 of them finding significant associations with outcome measures, namely, physiological status (VO_2max), quality of life, and functional status at discharge. However, measurement of echointensity is more technically demanding and depends on ultrasound frequency, gain, tissue depth, and the analysis technique used. Several studies have offered a standardized technique to improve reproducibility, but further research is required to correlate ultrasound echogenicity with current reference techniques such as CT radiodensity.

Finally, most of the studies in this review found a significant correlation between ultrasound metrics and outcome measures with only nine negative studies. Publication bias, with the underreporting of negative studies, remains a significant possibility that requires acknowledgement. It is therefore important that negative ultrasound research is also published alongside positive studies to improve our understanding of the technique and its generalizability in clinical practice.

Conclusions

This review has shown that SMUS has been used to assess muscle quality and quantity across a broad range of clinical settings and can detect alterations in muscle during a disease course. Ultrasound metrics such as muscle thickness, CSA, and echointensity have been used to predict clinical and functional outcomes in both acute and chronic clinical conditions. Muscle ultrasound continues to gain momentum as a bedside tool to quantify and monitor skeletal muscle. However, firm conclusions from this review are hindered by the heterogeneity and lack of standardized technique. Continued research is therefore required to further validate and standardize the technique, but also to establish cut-off values in different clinical populations. Further longitudinal research is also required in other cohorts, especially in clinical conditions where the prevalence of malnutrition and sarcopenia are high, such as patients with cancer.

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Conflict of interest

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