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Original article

Criterion validity of muscle strain analyses of skeletal muscle function in patients with multiple sclerosis

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A R T I C L E I N F O

Keywords:
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Muscle function

A B S T R A C T

Background: Despite the wide range of existing performance measures to evaluate functional status of patients with multiple sclerosis, the heterogeneous nature of the disease hinders clinical characterization and monitoring of disease severity. Speckle tracking ultrasonography is a non-invasive technique to assess isolated muscle function by evaluating the contractile properties of muscle tissue, i.e. muscle strain. The aim of this study was to investigate whether muscle strain measured by speckle tracking ultrasonography could be a useful quantitative measure of muscle function in patients with multiple sclerosis. The criterion validity of muscle strain was compared to that of validated performance measures of upper and lower extremity function.

Methods: This cross-sectional study used baseline data from an explorative observational cohort study (the MUST study). Participants recruited from a hospital outpatient MS clinic underwent speckle tracking ultrasonography of the biceps brachii, supraspinatus, and soleus muscles of the dominant side according to pre-defined sub-maximal isometric contractions. Participants also completed the Timed 25-Foot Walk Test, the Six Spot Step Test, the 2-minute walking test, the Nine-Hole Peg Test, the 12-item Multiple Sclerosis Walking Scale, and the Oxford Shoulder Score. Gaussian distribution was investigated by visual inspection of normal probability plots and the Shapiro-Wilk test. The Timed 25-Foot Walk Test and Nine-Hole Peg Test were selected as gold standards for function of the lower and upper extremities, respectively. Criterion validity was assessed using Spearman's rank-order correlation coefficient ρ (rho), comparing the muscle strain and performance measures against predefined gold standards. Differences in criterion validity were estimated using squared correlations on the Fischer's Z-scale, with non-parametric bootstrapping to obtain bias-corrected, accelerated bootstrap confidence intervals (95% BCa).

Results: Criterion validity showed good to excellent correlations between the gold standard for lower extremity function and the 2-minute walking test and Six Spot Step Test, and a fair correlation to the 12-item Multiple Sclerosis Walking Scale. No significant correlation was found between the gold standard for upper extremity function and the performance measure. There were no significant correlations between the gold standards and muscle strain.

Conclusion: The absence of criterion validity for muscle strain alongside fair to strong criterion validity for the performance measures indicates that speckle tracking ultrasonography assessment of muscle strain is either invalid or evaluates other constructs of multiple sclerosis. Muscle strain assessed by speckle tracking

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ultrasonography cannot be recommended for the evaluation of treatment effects or disease progression in multiple sclerosis.

Abbreviation

BB	Biceps brachii muscle
MVC	Maximal voluntary isometric contraction
OSS	Oxford Shoulder Score
PwMS	Patients with MS
SOL	Soleus muscle
SS	Supraspinatus muscle
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
STU	Speckle tracking ultrasonography
95% BCa	Accelerated bootstrap confidence interval
%MVC	Percentage of maximal voluntary contraction

1. Introduction

Despite effective treatments, quality of life is often affected in patients with multiple sclerosis (PwMS) due to impaired physical functions (Heesen et al. 2008). Up to 76% of patients use a walking aid or wheelchair, (Hobart et al. 2001) while approximately 75% of patients have bilaterally impaired manual dexterity (Bertoni et al. 2015).

Several validated performance measures are available to evaluate functional status in PwMS. The Timed 25-Foot Walk Test (T25FW) is a sensitive and reliable measurement of walking speed (Kalinowski et al. 2022) in PwMS. It is considered one of the best objective assessments of walking disabilities (Kieseier and Pozzilli 2012) and the closest to a gold standard of gait performance in multiple sclerosis (MS). The Six Spot Step Test (SSST) (Nieuwenhuis et al. 2006), is a measure of ambulatory speed, co-ordination, and balance (Nieuwenhuis et al. 2006, Sandroff et al. 2015), the 2 minute walking test (2MWT) assesses walking speed and endurance (Gijbels, Eijnde, and Feys 2011, Scalzitti et al. 2018), and the 12-item Multiple Sclerosis Walking Scale (MSWS-12) measures self-perceived impact of MS on gait function (Motl and Snook 2008). Furthermore, the Nine-Hole Peg Test (9HPT) assesses upper extremity motor function and is considered gold standard for evaluating manual dexterity in PwMS (Feys et al. 2017).

The clinical characterization of MS and monitoring of disease severity remain challenging (Albrecht et al. 2001, Filippi et al. 2018) however, and assessment of isolated muscle function may provide a more objective measure of functional status in PwMS, than the well-known clinical and performance measures.

Speckle tracking ultrasonography (STU) enables non-invasive quantification of regional muscle function by evaluating the contractile properties of muscle tissue, i.e. muscle strain (Frich et al. 2019). STU is widely used for dynamic myocardium examination (Mondillo et al. 2011) but has recently proven feasible for evaluating skeletal muscle of the upper extremity in healthy individuals (Frich et al. 2019) and patients with whiplash-associated disorders (Rahnama et al. 2018).

The objective of the current study was to investigate whether muscle strain measured by STU could be a useful quantitative measure of muscle function in PwMS. Criterion validity was assessed by correlating muscle strain to predefined gold standards for performance within the patient group. The criterion validity of muscle strain was then compared against the criterion validity of other well-known performance measures.

2. Materials and Methods

2.1. Participants and setting

The current cross-sectional study used baseline data from a larger explorative observational cohort study (the MUST study) (Trial registration: ClinicalTrials.gov NCT03847545). As described elsewhere (Skov et al. 2022, Thorning et al. 2022) the study was conducted at Odense University Hospital, Denmark from December 2018 to March 2021 and is reported according to the “STROBE statement” for reporting of observational studies (Vandenbroucke et al. 2007).

The study was approved by the National Committee on Health Research Ethics (S-20170203) and reported to the Danish Data Protection Agency (2012-58-0018). It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent prior to inclusion.

Eligible participants, for the MUST study, were recruited from the outpatient MS Clinic at Odense University Hospital. Inclusion criteria were a clinical diagnosis of MS according to the McDonald criteria (McDonald et al. 2001), age ≥18 years, and an Expanded Disability Status Score (EDSS) between 4 and 7. Exclusion criteria were diagnosed epilepsy, cancer within the last five years, clinically significant systemic disease, concurrent treatment with cimetidine, carvedilol, propranolol or metformin, change in immunomodulatory treatment within the last 60 days, MS attacks or acute decrease of functional capacity within 60 days (Skov et al. 2022, Thorning et al. 2022).

Participants underwent a 2–3-hour test session. Tests were conducted in the same order and obtained from the same experienced assessors. Walking aids were used as required for the individual tests. Baseline data were collected on gender, disease duration, sub-diagnosis, EDSS, and disease-modifying treatment.

2.2. Outcome measures

2.2.1. Muscle strain analysis

2.2.1.1. Dynamometry. For detailed description of the dynamometry, see Supplementary, Section 1.

Standardized STU was performed for the biceps brachii (BB), supraspinatus (SS), and soleus (SOL) muscles of the dominant side, according to pre-defined submaximal target force contractions (percentage of maximal voluntary contractions (%MVC)). The maximal voluntary isometric contraction (MVC) and subsequent submaximal isometric contractions were evaluated using a custom-made dynamometry (Force Transducer, U9C, ≥2kN, Hottinger Baldwin Messtechnick GmbH, Darmstadt, Germany). The MVC was established as the highest force output of three separate contractions and was used as reference for the %MVC during strain measurements. For the BB and the SOL, tests were performed at 20, 40, and 60 %MVC and for the SS at 40, 60, and 80 %MVC. For each submaximal intensity, participants were instructed to perform three isometric contractions at approximately 1 min intervals. Only recordings where %MVC was achieved within a margin of ±5% were included for further analysis.

The dynamometry was connected to a computer through a combined Wheatstone bridge, 24 bit analogue-to-digital converter (cDAQ-9174/NI-9237, National Instruments, Austin, TX, USA) using custom-developed software (Labview Runtime Engine 2017, National Instruments, Austin, TX, USA). The %MVC was displayed together with the actual force trajectory applied by the participant in real-time in the form of a biofeedback curve on a monitor (Supplementary Fig. 1).

2.2.1.2. Speckle tracking ultrasonography (STU). For detailed description of STU, see Supplementary, Section 2.

In synchrony with force contractions, STU was performed with a Vivid S70 ultrasound scanner (General Electric Healthcare, Horton, Norway) using a M11 L-MHz linear transducer. During recordings, the position of the ultrasound transducer was kept unchanged relative to the skin. Participants were seated in a stable upright position and strapped to the dynamometry, ensuring the stability of the patient to avoid out-of-plane motion (Supplementary Figs. 2-4). Anatomical landmarks were identified and marked to standardize the transducer placement. To overcome the influence of muscle fibre pennation, the transducer was oriented parallel to the loading axis of the individual muscle.

The recorded ultrasound data were analysed offline using speckle tracking software (EchoPAC Software Only v203, General Electric Healthcare, Horton, Norway), specifically the two-dimensional strain modality of the Q-analysis function, as previously described (Frich et al. 2019). The same investigator performed all strain analyses using a standardized protocol.

A region of interest (ROI) was manually placed within the muscle to register the longitudinal muscle changes (Supplementary Fig. 4). Peak muscle strain was registered as the relative change between speckles inside a specified ROI, where negative values refer to shortening of the muscle. (Lang et al. 2015, Voigt et al. 2015). Higher negative values represent higher muscle strain.

2.2.2. *Performance measures*

Gait function was assessed as described in previous manuscripts founded in the MUST study (Skov et al. 2022, Thorning et al. 2022), using the following measures: *i*) The T25FW (Fischer et al. 1999), where participants were instructed to walk as fast as possible on a 25 foot course, according to the Multiple Sclerosis Functional Composite (Fischer et al. 2001); *ii*) The SSST which consisted of criss-cross walking on a rectangular course while kicking five blocks out of marked circles on the floor and in the fastest time possible (Nieuwenhuis et al. 2006); *iii*) The 2MWT (Gijbels, Eijnde, and Feys 2011), where participants were instructed to walk as far as possible for two minutes while walking laps on a 20 m lane (Gijbels, Eijnde, and Feys 2011); and *iv*) the MSWS-12, where participants rated the impact of MS on their walking ability; the total score was transformed to a scale from 0 to 100 (minimum to maximum walking disability) (Hobart et al. 2003).

Upper extremity function was evaluated using the 9HPT according to the Multiple Sclerosis Functional Composite (Fischer et al. 2001). Participants who had had shoulder problems for more than two weeks prior to inclusion also self-completed the 12-item Oxford Shoulder Score (OSS), which is designed to evaluate treatment of shoulder conditions (Frich, Noergaard, and Brorson 2011).

2.3. *Statistical analysis*

Gaussian distribution of the data was investigated by visual inspection of normal probability plots and the Shapiro-Wilk test. Descriptive statistics are reported as mean values and standard deviations (SD) or median values and interquartile range (IQR). The statistical analyses were performed using Stata/BE 17.0 (StataCorp LLC, College Station, TX, USA).

The T25FW and the 9HPT were selected as gold standards for function of the lower and upper extremities, respectively. Criterion validity was assessed by investigating correlations between the gold standards and muscle strain or performance measures. For unilateral tests, including STU, the dominant side was analysed.

To evaluate criterion validity, scatter plots were examined, and linear regressions for performance measures and muscle strain were fitted, using gold standards as the dependant variables. Because the residuals and fitted regression values showed that assumptions for a linear regression model (normality of error terms and homoscedasticity) were not met, criterion validity was evaluated using the Spearman's rank-order correlation coefficient ρ (rho). The correlation coefficients were interpreted as: little to no relationship ($r = 0.00$ to 0.25), fair relationship ($r = 0.25$ to 0.50), moderate to good relationship ($r = 0.50$ to 0.75), and good to excellent relationship ($r > 0.75$) (Portney 2008).

We then evaluated whether muscle strain or performance measures had the highest criterion validity, taking the insecurities of the correlations into account.

Bootstrapping was applied as correlation estimates from the same participants cannot be assumed to be independent (Cohen 1989). We estimated the difference in criterion validity as squared correlations on the Fischer's Z-scale and used non-parametric bootstrapping to obtain bias-corrected, accelerated Bootstrap Confidence Intervals (95% BCa). We used the 95% BCa to evaluate the null hypothesis that the difference was zero, i.e. that the two correlations had the same absolute value. If 95% BCa encompassed zero, we could not reject the null hypotheses. If 95% BCa was negative, criterion validity for the performance measures was higher than that of muscle strain. If 95% BCa was positive, muscle strain had higher criterion validity than the performance measures.

3. Results

Of 71 eligible patients, 43 were included in the current analyses. Sixteen patients declined participation, eight did not meet inclusion criteria, three participants were not allocated to STU, and baseline data was missing for one participant (Fig 1).

Average age (±SD) of the participants was 54.9 (11.6) years, 58.1% were female and median [IQR] EDSS was 6.0 [5.0/6.5], see Table 1. Mean (±SD) MS duration was 19 (±10) years, and 44-61% used walking aids during testing, see Table 1. Amongst the performance measures, missing data were primarily in the OSS, while 1–7% had missing data in the %MVC categories in STU.

Regarding criterion validity, no significant correlations were found between the gold standards and muscle strain for either lower extremity or upper extremity (p>0.05) (Table 2). For the lower extremity correlations between gold standards and performance measures were good to excellent between T25FW and 2MWT, as well as T25FW and SSST, and there was a fair correlation between T25FW and MSWS-12 (Table 3). Conversely, no significant correlations were detected for the upper extremity between gold standard and the performance measure OSS (p>0.05) (Table 2).

For all criterion validity comparisons between the MSWS-12 and muscle strain, the 95% BCa encompassed zero. The null hypothesis could thus not be rejected, and it was inconclusive whether muscle strain or MSWS-12 had the highest criterion validity for measuring muscle function in PwMS (Table 3). In the other comparisons for the lower extremity, performance measures showed higher criterion validity to evaluate muscle function in PwMS than muscle strain (Table 3). All criterion validity comparisons in the upper extremity were inconclusive.

Within individual participants, muscle strain showed large intra-session variability causing sizeable SD and IQR for all included muscles and %MVC (Table 4). In the lower extremity, STU of the SOL demonstrated higher muscle strain values with higher %MVC. In the upper extremity, STU for both BB and SS showed similar increased muscle strain between low and moderate %MVC (BB: 20 %MVC to 40 % MVC; SS: 40 %MVC to 60 %MVC) after which muscle strain showed a tendency to stagnate with higher %MVC (BB: 60 %MVC; SS: 80 %MVC) (Table 4).

4. Discussion

This study has explored the criterion validity of STU in PwMS by using muscle strain to quantitatively measure muscle function. With the T25FW and 9HPT as gold standards for function of the lower and upper extremities, criterion validity showed good to excellent correlations for the lower extremity between the gold standard and 2MWT and SSST, and fair correlation with MSWS-12. No significant correlations were found between the gold standard and performance measures for the upper extremity. Additionally, criterion validity demonstrated no significant correlations between gold standards and muscle strain.

Although all our participants had walking impairments due to MS, muscle strain in the lower extremity appeared to increase with higher %

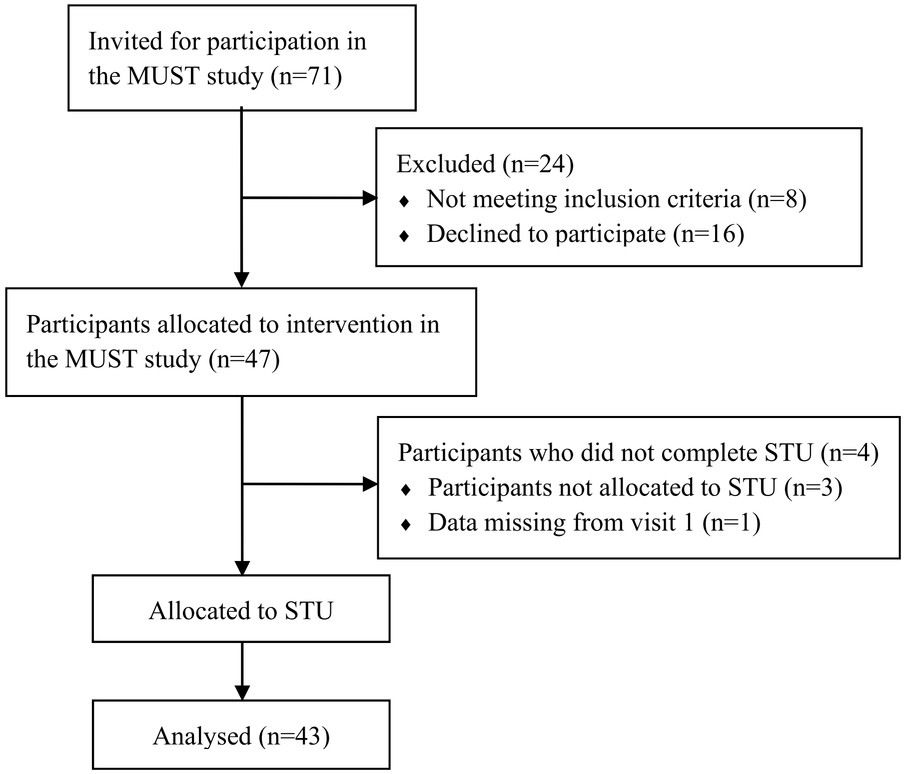

Fig 1. Flowchart of participant inclusion in the sub-study exploring speckle tracking ultrasonography (STU).

Table 1
Characteristics of the participants (n=43)

Characteristic	
Age, years	54.9 (11.6)
Females, n (%)	25 (58.1)
Multiple sclerosis duration, years	19.2 (9.5)
Sub-diagnosis, n (%)	
Relapsing-Remitting	19 (44.2)
Secondary Progressive	17 (39.5)
Primary Progressive	7 (16.3)
Disease-modifying treatment, n (%)	
Aubagio	6 (14.0)
Tecfidera	6 (14.0)
Tysabri	2 (4.7)
Gilenya	2 (4.7)
Lemtrada	1 (2.3)
Copaxone	2 (4.7)
Rebif	1 (2.3)
Ocrevus	7 (16.3)
Rituximab	4 (9.3)
No treatment	12 (27.9)
EDSS	6.0 [5.0/6.5]
Patients using walking aids during the following tests, n (%)	
T25FW	19 (44.2)
SSST	20 (46.5)
2MWT	26 (60.5)

Values are mean (SD), median [IQR], or n (%)
EDSS: Expanded Disability Status Score; MSWS-12: 12-item MS Walking Scale; n: number; SD: standard deviation; SSST: Six Spot Step Test; T25FW: Timed 25-Foot Walk; 2MWT: 2-Minute Walk test.

Table 2
Spearman's rank order correlations ρ (rho) between gold standards and i) performance measures and ii) muscle strain.

Measure	Dependent variable	Numbers (n)	Spearman's ρ (rho)	p-value
Muscle strain, LE				
	Variable correlated with T25FW (gold standard, LE)			
	SOL20 %MVC	39	-0.12	0.47
	SOL40 %MVC	40	0.04	0.81
	SOL60 %MVC	39	0.02	0.92
Performance measures, LE				
	SSST	43	0.84	0.00
	2MWT	43	-0.93	0.00
	MSWS-12	42	0.35	0.03
Muscle strain, UE				
	Variable correlated with 9HPT (gold standard, UE)			
	BB20 %MVC	36	-0.07	0.68
	BB40 %MVC	41	-0.13	0.40
	BB60 %MVC	41	-0.17	0.29
	SS40 %MVC	36	-0.21	0.21
	SS60 %MVC	39	-0.21	0.19
	SS80 %MVC	40	-0.13	0.43
Performance measure, UE				
	OSS	10	0.31	0.38

BB: biceps brachii muscle; LE: lower extremity; MSWS-12: 12-item MS Walking Scale; %MVC: submaximal target force; n: number; 9HPT: Nine-Hole Peg Test; OSS: Oxford Shoulder Score; SD: standard deviation; SOL: soleus muscle; SSST: Six Spot Step Test; SS: supraspinatus muscle; T25FW: Timed 25-Foot Walk; 2MWT: 2-Minute Walk test; UE: upper extremity.

MVC even when %MVC exceeded moderate load (40 %MVC for SOL). In contrast, the upper extremity showed a tendency towards stagnation of muscle strain when %MVC exceeded moderate load (40 %MVC for BB; 60 %MVC for SS). Our lab has previously shown that muscle strain in the upper extremity of healthy individuals increases with increasing load (% MVC) (Frich et al. 2019). However, the muscle strain we measured for low and moderate muscle contractions in the upper extremity was lower compared to a healthy population (Frich et al. 2019). This was expected due to reduced muscle strength in PwMS (Pau et al. 2014), and the relative submaximal loads from MVC testing reflect absolute lower loads in our sample.

The muscles investigated in this study were selected due to their accessibility and functional relevance. In the lower extremity of PwMS, muscle strength of several muscle groups (e.g. the hip abductors

Table 3
Comparison of criterion validity between muscle strain and performance measures using squared correlations on the Fischer's Z-scale.

	Numbers (n)	Z-difference coefficient	95% BCa CI	Conclusion
Variables compared, LE				
T25FW; SOL20 %MVC vs. T25FW; SSST	39	-0.81	[-1.26; -0.42]*	In favour of PM
T25FW; SOL20 %MVC vs. T25FW; MSWS-12	38	-0.08	[-0.43; 0.09]	Inconclusive
T25FW; SOL20 %MVC vs. T25FW; 2MWT	39	-1.31	[-1.73; -0.91]*	In favour of PM
T25FW; SOL40 %MVC vs. T25FW; SSST	40	-0.85	[-1.31; -0.41]*	In favour of PM
T25FW; SOL40 %MVC vs. T25FW; MSWS-12	39	-0.13	[-0.45; 0.02]	Inconclusive
T25FW; SOL40 %MVC vs. T25FW; 2MWT	40	-1.31	[-1.72; -0.96]*	In favour of PM
T25FW; SOL60 %MVC vs. T25FW; SSST	39	-0.79	[-1.24; -0.39]*	In favour of PM
T25FW; SOL60 %MVC vs. T25FW; MSWS-12	38	-0.09	[-0.40; 0.04]	Inconclusive
T25FW; SOL60 %MVC vs. T25FW; 2MWT	39	-1.25	[-1.64; -0.85]*	In favour of PM
Variables compared, UE				
9HPT; OSS vs. 9HPT; BB20 % MVC	8	-0.09	[-1.61. 0.54]	Inconclusive
9HPT; OSS vs. 9HPT; BB40 % MVC	10	0.17	[-0.30; 1.45]	Inconclusive
9HPT; OSS vs. 9HPT; BB60 % MVC	10	0.16	[-0.97; 1.50]	Inconclusive
9HPT; OSS vs. 9HPT; SS40 % MVC	8	-0.72	[-17.18; 0.08]	Inconclusive
9HPT; OSS vs. 9HPT; SS60 % MVC	9	-0.19	[-1.28; 0.72]	Inconclusive
9HPT; OSS vs. 9HPT; SS80 % MVC	9	-0.20	[-1.29; 0.65]	Inconclusive

Notes:
Non-parametric bootstrapping was used to obtain accelerated 95% bootstrap confidence intervals (95% BCa) as correlation estimates from the same patient could not be assumed to be independent. 95% BCa followed by * indicates a statistically significant difference in criterion validity.
If 95% BCa encompassed zero, we cannot reject the null hypotheses that the correlations are identical (*inconclusive*). If 95% BCa is negative, the performance measure (PM) has higher criterion validity than muscle strain (*in favour of performance measure*). If 95% BCa is positive, muscle strain has higher criterion validity than performance measures (*in favour of muscle strain*).
BB: biceps brachii muscle; LE: lower extremity; MSWS-12: 12-item MS Walking Scale; %MVC: submaximal target force; n: number; 9HPT: Nine-Hole Peg Test; OSS: Oxford Shoulder Score; SD: standard deviation; SOL: soleus muscle; SSST: Six Spot Step Test; SS: supraspinatus muscle; T25FW: Timed 25-Foot Walk; 2MWT: 2-Minute Walk test; UE: upper extremity.

Table 4
Muscle strain and performance measures at baseline in participants with multiple sclerosis.

Measure	Variable	Numbers (n)	Muscle strain (%)
Muscle strain, LE			
	SOL20 %MVC	39	-12.64 (7.67)
	SOL40 %MVC	40	-17.79 (10.38)
	SOL60 %MVC	39	-22.12 [-27.12/-16.51]
Muscle strain, UE			
	BB20 %MVC	36	-10.86 (6.76)
	BB40 %MVC	41	-13.58 (7.33)
	BB60 %MVC	41	-13.53 (7.56)
	SS40 %MVC	36	-8.71 (5.48)
	SS60 %MVC	39	-9.82 [-12.28/-3.0]
	SS80 %MVC	40	-9.53 (6.05)
Performance measures, LE			
	T25FW	43	7.35 [6.1/9.1]
	SSST	43	13.03 [10.0/17.48]
	2MWT	43	111.61 (36.89)
	MSWS-12	42	67.41 (17.01)
Performance measures, UE			
	9HPT	43	24.8 [22/30.15]
	OSS	10	23 [23/26]

Values are reported as mean (SD) or median [IQR].
BB: biceps brachii muscle; LE: lower extremity; MSWS-12: 12-item MS Walking Scale; %MVC: submaximal target force; n: number; 9HPT: Nine-Hole Peg Test; OSS: Oxford Shoulder Score; SD: standard deviation; SOL: soleus muscle; SSST: Six Spot Step Test; SS: supraspinatus muscle; T25FW: Timed 25-Foot Walk; 2MWT: 2-Minute Walk test; UE: upper extremity.

(Mañago et al. 2018), knee flexors (Broekmans et al. 2013, Callesen et al. 2019, Kjølhede et al. 2015), knee extensors (Broekmans et al. 2013, Callesen et al. 2019, Kjølhede et al. 2015), and ankle plantar flexors (Callesen et al. 2019, Wagner et al. 2014)) have previously demonstrated associations with gait speed and walking endurance. In the present study, we chose to examine the SOL as it is the primary contributor to forward propulsion of the limb (McGowan, Neptune, and Kram 2008) and has a more important functional role than the gastrocnemii muscles, especially in walking for prolonged periods and at faster speeds (Cronin et al. 2013). Muscle strain of other primary movers in the lower extremity could be interesting to examine, however.

PwMS have less muscle strength in the upper extremity compared to healthy individuals (Ingram et al. 2022, Jørgensen et al. 2017), but few studies have examined this muscle function in PwMS more closely (Jørgensen et al. 2017). The present study investigated muscle strain during submaximal isometric contractions of the BB and the SS, which are both easily accessible to STU and are either a primary mover of elbow flexion (BB) or important for shoulder stability (SS). Furthermore, a correlation has been reported between muscle strength of elbow flexion and the 9HPT (Guclu-Gunduz et al. 2012), which is a measure of manual dexterity and upper extremity function in PwMS (Feys et al. 2017). This association confirms the relevance of using the 9HPT as gold standard for upper extremity function, though it does not explain the lack of significant correlations when we compared the criterion validity of STU.

STU is a new method for evaluating skeletal muscles in PwMS. The lack of significant correlations between muscle strain and gold standards could be due to the large intra-session variability in muscle strain within individuals, for all muscles and %MVC. This may have stemmed from the heterogeneity of MS (Filippi et al. 2018), with large day-to-day variability in general performance (Albrecht et al. 2001). Furthermore, the STU setup was standardized for all participants, but we cannot exclude that results may change with a different setup. We used commercial speckle tracking software based on algorithms developed for myocardium, which is thus designed to measure longitudinal movements of targeted muscles in two dimensions. This may limit the ability to capture the specific speckle and motion patterns that are common in skeletal muscles, including rotational movements. Similar methodologies using commercial speckle tracking software to examine skeletal muscle strain have been applied in previous studies, however. We have previously demonstrated satisfactory criterion validity in the BB and SS muscles in healthy subjects when correlating muscle strain to external load (Frich et al. 2019), and Gao et al. (Gao et al. 2019) found significant higher strain-rate values (peak muscle strain divided by peak strain of subcutaneous tissue, used as reference) in the BB and gastrocnemius muscles in PwMS compared to healthy individuals. These assessments were performed during passive flexion of the elbow and plantarflexion of the ankle, however, so a direct comparison to our results is difficult. In addition, the comparison between PwMS and healthy individuals does not indicate responsiveness, i.e. the ability of a measure to evaluate change following an intervention.

In the lower extremity, the good to excellent correlations between T25FW and SSST and 2MWT are similar to previous studies (Bennett et al. 2017, Nieuwenhuis et al. 2006, Sandroff et al. 2015, Sandroff et al. 2021), confirming good criterion validity of these functional performance measures in evaluating gait in PwMS. The fair correlation between T25FW and MSWS-12 detected in the present study was lower than correlations previously reported ranging between 0.57 and 0.73 (Bennett et al. 2017, Motl et al. 2013, Pilutti et al. 2013). Nevertheless, criterion validity of the MSWS-12 for evaluating gait in PwMS is still significant, albeit weaker than the other functional performance measures that were investigated. This could explain why comparisons of criterion validity was inconclusive to whether muscle strain or the MSWS-12 had the highest criterion validity, when all other performance measures of the lower extremity displayed higher criterion validity to evaluate muscle function in PwMS than muscle strain. It could moreover, indicate that MSWS-12 measures different aspects of walking compared to the included functional performance measures (Kieseier and Pozzilli 2012).

We found no significant correlation between the 9HPT and the OSS, possibly because the OSS is a self-completed measure validated for patients with inflammatory or degenerative shoulder disease (Frich, Noergaard, and Brorson 2011). It would be useful for future studies to consider other self-completed measures of upper extremity function validated in PwMS. The lack of significant findings when comparing the criterion validity of OSS versus muscle strain might be due to the very low number of participants who completed the OSS for the STU test side.

The T25FW has previously shown to be valid and reliable in evaluating gait speed in PwMS (Kalinowski et al. 2022), and our findings of significant correlations between T25FW and SSST, 2MWT, and MSWS-12 imply that T25FW is relevant as a gold standard. The T25FW does not measure the individual's ability to vary the gait according to different tasks required during walking (Bennett et al. 2017) however, so it can rarely stand alone as a measure of lower extremity function. Similarly, 9HPT has excellent properties of reliability and validity and is considered a gold standard for manual dexterity in PwMS (Feys et al. 2017). The 9HPT does not include all relevant domains of upper extremity function, however (Kraft et al. 2014). Therefore, a comprehensive evaluation of upper and lower extremity function in PwMS calls for a combination of measures, which is time-consuming and not easily applicable in clinical practice. Our results indicate that STU in its current form presents many methodological issues, and it cannot yet be seen as a feasible measure for evaluating function in PwMS nor as a substitute for a comprehensive test battery.

4.1. Limitations

As the present study used baseline data from an explorative observational cohort study with a different aim, we could not perform an a priori sample size calculation for the criterion validity analyses. The study also had missing data, where 1-7% of data for each %MVC category were missing. The number of approved trials for the %MVC of each muscle varied due to low quality of the STU assessments or because the visual biofeedback was difficult to comprehend for some participants. Furthermore, some experienced challanges in obtaining the individual %MVC, but repetitive testing resulted in only few participants missing in each category. Some participants experienced pain and/or functional problems and could not complete the testing. Missing data were mainly in the OSS as only few participants experienced shoulder problems at the STU test side. While comparisons on the lower extremity could be made on 38–40 individuals with complete data, only 8–10 participants had full data for the upper extremity. This may explain the non-significant correlations between the gold standard (9HPT) and both muscle strain and OSS, as well as the inconclusive results in the comparisons of criterion validity between muscle strain and OSS.

5. Conclusion

The current non-significant criterion validity for muscle strain in lower and upper extremities and fair to strong criterion validity for the performance measures indicate that the present methodologies of using muscle strain is either invalid or evaluates other constructs of MS otherwise not shown by standard test procedures. Therefore, muscle strain assessed by STU in its present form cannot be recommended for the evaluation of treatment effects or disease progression in PwMS.

6. Author contribution

Conception or design of the work: MT, HHN, AHL, KLL, LHF, HBJ
Coordinating the study: MT, HHN
Data collection: MT, CDS
Data-analysis: MT
Interpretation of data: MT, HHN, AHL, KLL
Writing – drafting the work: MT, HHN, AHL, KLL
Writing – Revision and editing of the work: All
Final approval of the version to be published: All

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Declaration of competing interest

MT and CDS declares no conflict of interest. LHF, KLL and AHL have an ongoing patent application in USA for the speckle tracking ultrasonography method used in the present study: Patent application no. 16/482,550. HHN and HBJ have received financial compensation for travels, consultations, and advisory boards from Biogen Idec, Roche, Sanofi Genzyme, Merck & Co Inc., Novartis, and Teva.

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Trial registration

ClinicalTrials.gov NCT03847545

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104478.

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