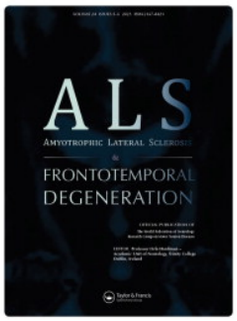

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Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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To cite this article: Jordi W. J. Van Unnik, Jaap N.E. Bakers, Steure Kokx, Leonard H. Van Den Berg, Johanna M.A. Visser-Meily, Anita Beelen & Ruben P.A. Van Eijk (2023): Portable fixed dynamometry enables home-based, reliable assessment of muscle strength in patients with amyotrophic lateral sclerosis: a pilot study, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2023.2231494

To link to this article: https://doi.org/10.1080/21678421.2023.2231494

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2023; 0: 1–10

RESEARCH ARTICLE

Portable fixed dynamometry enables home-based, reliable assessment of muscle strength in patients with amyotrophic lateral sclerosis: a pilot study

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Abstract

Objective: To determine the feasibility, reliability, and sensitivity of remotely monitoring muscle strength loss of knee extensors using a novel portable fixed dynamometer (PFD) in patients with amyotrophic lateral sclerosis (ALS). *Methods:* We conducted a pilot study with a newly developed device to measure knee extension strength. Patients performed unsupervised PFD measurements, biweekly, for 6 months at home. We evaluated feasibility using adherence and a device-specific questionnaire. Reliability was assessed by (1) comparing unsupervised and supervised measurements to identify systematic bias, and (2) comparing consecutive unsupervised measurements to determine test-retest reliability expressed as intraclass correlation coefficient (ICC) and standard error of measurement (SEM). Sensitivity to detect longitudinal change was described using linear mixed-effects models. *Results:* We enrolled 18 patients with ALS. Adherence was 86%, where all patients found that the device suitable to measure muscle strength at home; 4 patients (24%) found the measurements burdensome. The correlation between (un)supervised measurements was excellent (Pearson's r 0.97, 95%CI; 0.94 – 0.99) and no systematic bias was present (mean difference 0.13, 95%CI; −2.22 – 2.48, $p = 0.91$). Unsupervised measurements had excellent test-retest reliability with an average ICC of 0.97 (95%CI: 0.94 – 0.99) and SEM of 5.8% (95%CI: 4.8 – 7.0). Muscle strength declined monthly by 1.9 %predicted points (95%CI; −3.0 to −0.9, $p = 0.001$). *Conclusions:* Using the PFD, it proved feasible to perform knee extension strength measurements at home which were reliable and sensitive for detecting muscle strength loss. Larger studies are warranted to compare the device with conventional outcomes.

Keywords: *Fixed dynamometry, amyotrophic lateral sclerosis, muscle strength, feasibility study, remote monitoring*

Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive loss of motor neurons, resulting in severe muscle weakness and limitations in daily life (1). Assessment of muscle strength, therefore, plays a pivotal role in ALS clinical trials and care (2–7). Common methods of muscle strength assessment range from manual muscle testing, using subjective scales, to more objective dynamometry (3–5). Hand-held dynamometry (HHD) is frequently used. It has many advantages compared to manual scales, but can be improved by using a fixed construction (8,9). By fixating the dynamometer, the measurement no longer relies on the examiner's strength and the overall standardization of the

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21678421.2023.2231494.

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(Received 15 March 2023; revised 16 May 2023; accepted 14 June 2023)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2023.2231494

test is improved. This prevents possible ceiling effects and reduces variability (10,11).

The major downside, however, is that systems for fixed dynamometry currently available are for in-clinic use only (12–19). Especially for diseases like ALS, in-clinic visits impose a substantial burden on patients. This not only results in early dropout, attrition and loss-to-follow-up (20), it also affects the willingness of patients to participate in clinical trials or to attend multidisciplinary care clinics (21–23). Furthermore, patients report that muscle strength, together with respiratory function, is the most important outcome for home-monitoring (24). Enabling patients to monitor their muscle strength remotely, outside the hospital setting, may, therefore, improve patient enrollment and retention, and facilitate a patient-centric clinical trial and care model (25). In addition, variability in outcomes may be reduced by increasing the sampling frequency, which would be more feasible with home-based assessments (26).

To transition toward remote monitoring of muscle strength, we previously developed a portable fixed dynamometer (PFD) to quantify knee extension strength. Assessment of the knee extensors was chosen as their function remains measurable for a relatively long time, thereby minimizing potential floor effects, and their decline in strength has been well correlated to other clinically relevant outcomes (5,27,28). In-clinic use of the device showed excellent reliability of supervised measurements in patients with ALS (11), and has now been modified to allow for home-based unsupervised measurements. The aim of the present project was to conduct a pilot study to determine (1) the feasibility of performing home-based muscle strength measurements using the PFD, (2) the reliability of PFD measurements and (3) the PFD's sensitivity to detect muscle strength change over time. This study intended primarily to generate insights into potential challenges when using the device in clinical trials and to explore the extent to which home-based muscle strength measurements can be adopted in research and care.

Methods

Study design, setting and population

This prospective cohort study was performed at the University Medical Centre (UMCU), The Netherlands. Patients were included if they met the following criteria: (1) had a diagnosis of ALS according to the Gold Coast criteria (29), (2) were 18 years or older and (3) had an MRC of $\geq$ 3 in at least one leg. Patients were excluded if they had severe cognitive impairment, or had been diagnosed with frontotemporal dementia, or were experiencing recent or current knee pain. Patients with a history of knee trauma were not excluded, unless there was recent or current knee pain. All patients were recruited by their physiotherapist from the outpatient clinic of the UMCU. The study was approved by the Medical Ethics Committee of the UMCU (protocol number 21-333). All patients provided written informed consent to participate in this study.

Portable fixed dynamometer

The PFD is a portable device that assesses isometric muscle strength of the knee extensors (Figure 1). The device is placed in front of a (wheel) chair, then the vertical and horizontal arms of the device are aligned with the length of the patient's leg using two adjustment knobs. This prevents the feet from touching the ground and standardizes the starting position of the knee joint at 90 degrees. The construction was designed so that knee extension force pushes the device proportionally downwards onto the ground, stabilizing its position, and preventing the device from slipping or tilting (Figure 1(D)). Compared to our previous model (11), this prototype has integrated dynamometers, larger padded shin plates to distribute pressure and increase comfort, and a user interface to display instructions.

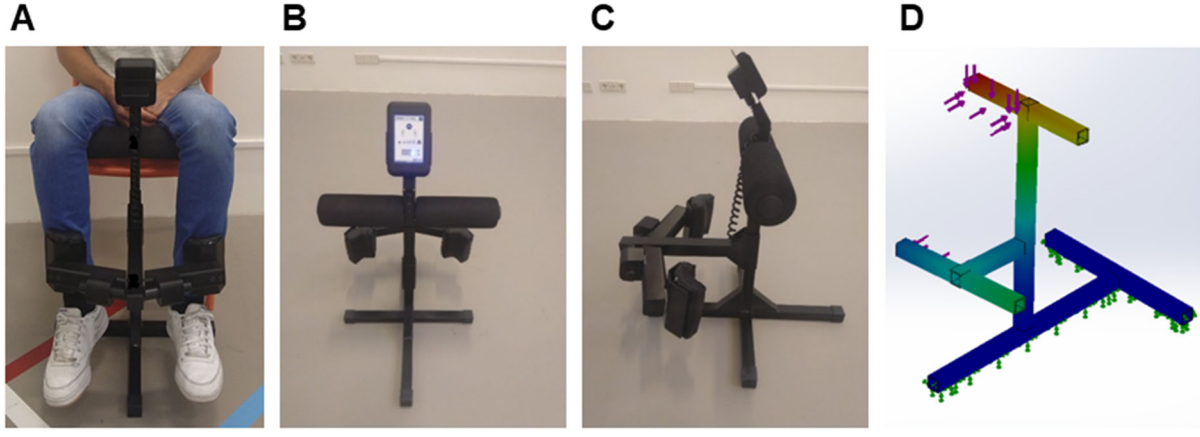

Figure 1. Improved prototype of the Portable Fixed Dynamometer (PFD). The improved PFD prototype with integrated dynamometers, padded shin plates and a user interface (A–C). Three-dimensional force analysis during assessment of the knee extensors (D). Arrows indicate the direction of the force (red indicates high force; blue indicates low force).

At the start of each measurement, the user interface illuminates a picture of the left or right foot, indicating the measurement side, and counts down from 10. During measurements, users are instructed to build up their strength during the first two seconds and exert their maximum force during the last second, as indicated by different LED colors and audio cues. After each measurement, the results are displayed in kilograms.

Study procedures

After collection of disease characteristics, patients were visited at home by the study examiner. During the first visit, the examiner adjusted device settings and provided instructions. Patients were trained by asking them to perform one supervised measurement cycle, consisting of three muscle strength measurements for each leg. Measurements were not recorded during this practise session, as it is likely that patients would be too fatigued, making the measurements unrepresentative. After 1 month, each patient was contacted to resolve potential issues. During follow-up, patients were asked to perform unsupervised muscle strength measurement cycles once every 2 weeks, for a maximum duration of 6 months. In addition, patients kept a diary to record pain or other factors that may have influenced the measurements. To improve adherence, patients were sent an e-mail reminder on the day before each scheduled measurement. In addition, they were sent a report every 3 months which provided personalized feedback on their muscle strength measurements. ALS functional rating scale (ALSFRS-R) scores were collected remotely every 4 weeks using the telehealth service *ALS Home-monitoring and Coaching* mobile app (30). At the last measurement cycle, both a supervised and an unsupervised measurement cycle was performed, together with the administration of a device-specific questionnaire (Supplemental online material 1). The questionnaire consisted of thirteen items using a five-point Likert scale and evaluated topics such as ease of use and burden (answer options: very easy—very difficult, or totally agree—totally disagree).

Muscle strength outcome

Muscle strength data were summarized in alignment with the standard operating procedures of TRICALS/ENCALS: for each leg, during each assessment, we selected the higher of the two closest scores of the three available measurements. For the resulting score of each leg, we then allocated the leg that had the higher score at baseline to the category "stronger," and the leg with the lower score to the category "weaker." We also calculated the mean score across legs. Muscle strength scores were subsequently standardized for sex, age, weight and height using a European reference cohort (31). These standardized scores are interpreted as the percent of predicted normal, similarly to the interpretation of %predicted vital capacity. The %predicted mean muscle strength score was selected as the primary PFD measurement.

Sample size

The sample size required for this study was based on the PRO-ACT database (version December 2015, available at https://ncri1.partners.org/proact) (32). In PRO-ACT, we observed a 0.31 (95%CI: $0.30 - 0.32$) point per month loss in ALSFRS-R gross motor functioning over the course of 6 months. In order to detect this rate of decline, with 80% power and a two-sided alpha of 5%, 18 patients would be needed and followed for 6 months at biweekly intervals (33).

Statistical analysis

Descriptive data were summarized using mean and standard deviation (*SD*), or median and range for continuous variables, and frequency and percentage for categorical variables. Feasibility was evaluated based on adherence and the device-specific questionnaire. Adherence was calculated as the number of completed PFD measurements divided by the total number of scheduled measurements.

Reliability was assessed by (1) comparing unsupervised and supervised PFD measurements at last measurement cycle to identify potential systematic bias, and (2) comparing consecutive unsupervised measurements to determine the measurement error during follow-up (test-retest reliability). For the comparison between unsupervised and supervised measurements, we calculated the Pearson's r between measurements obtained at last measurement cycle. Systematic bias was evaluated using a Bland-Altman plot and tested using a Student's T-test to evaluate whether the mean difference between unsupervised and supervised measurements differed from zero. The 95% limits of agreement was calculated after applying a 10log-scale transformation due to the heteroscedasticity in the data and was subsequently back-transformed to its original scale (34). For the unsupervised measurements, every two consecutive muscle strength scores were compared, if available. After applying the 10log-scale transformation, the intraclass correlation coefficient (ICC) was estimated using linear mixed-effects (LME) models incorporating only a fixed intercept and random intercept per patient (34). The ICC was then interpreted as the proportion of total variation (i.e., the sum of the between-subject and within-subject variation) that can be explained by the between-subject variation. The standard error of measurement (SEM) was calculated by taking the square root of the within-subject variation and was subsequently

Table 1. Demographics and clinical characteristics of study population.

Characteristic		$N = 17$
Age (years)	Mean (*SD*)	61 (9)
Sex	Men, *n* (%)	12 (71)
Body mass index (kg/m^2)	Mean (*SD*)	26 (4)
Symptom duration (months)	Median (range)	53 (11–389)
Diagnostic delay (months)	Median (range)	17 (4–167)
ΔFRS (points per months)	Median (range)	−0.23 (−1.40 to −0.01)
ALSFRS-R total score	Mean (*SD*)	37 (6)
Bulbar subdomain		10 (3)
Fine subdomain		8 (3)
Gross subdomain		9 (3)
Respiratory subdomain		10 (3)
VC, % predicted—GLI-2012	Mean (*SD*)	81 (21)
Missing	*n* (%)	1 (6)

Abs. ALSFRS-R: ALS functional rating scale; VC: vitality capacity.
ΔFRS = 48 - ALSFRS-R total score/symptom duration.

back-transformed to its original scale (34). The uncertainty around these estimations was determined by means of bootstrapping ($n = 10{,}000$).

Finally, to describe the sensitivity of the PFD for detecting longitudinal change, we examined the mean rate of decline in %predicted muscle strength and the ALSFRS-R, using LME models with a fixed effect for time and a random intercept and slope for time per patient. Analyses were conducted with R using the *lmer* function (R package lme4 version 1.1-27).

Results

Patient population and feasibility

A total of eighteen patients were enrolled between October 2021 and December 2021. One patient withdrew immediately after baseline because the device had fallen down the stairs, causing irreparable damage. The demographics and clinical characteristics of the remaining seventeen patients are described in Table 1. In these patients the disease was progressing relatively slowly with a change in the ALSFRS-R (ΔFRS) of 0.23 points per month. Of the 221 scheduled PFD measurements, 190 (86%) were completed, with individual adherence rates ranging from 38 to 100% (Figure 2). Total follow-up time was 90 patient-months, during which no occurrences of measurement-related cramps or knee pain were reported. One patient continued measuring only one leg because knee arthrosis was diagnosed in the other leg, and another patient was advised to discontinue because of deep-venous thrombosis in the lower leg. In two cases, a second home visit was performed to provide additional instructions. Fatigue across measurement attempts was evaluated by comparing the first and last repeat of each leg; we found no statistically significant differences (left leg mean difference −0.6 kg [95%CI: −1.3 to 0.1], $p = 0.11$; right leg mean difference −0.5 kg [95%CI: −1.2 to 0.2], $p = 0.16$).

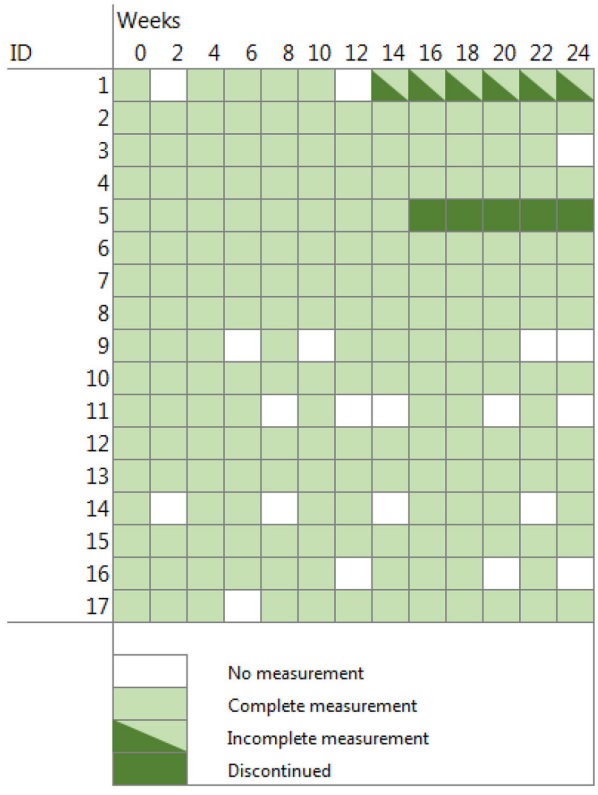

Figure 2. Adherence per patient. During follow-up, one patient (patient 1) continued measuring only one leg and another patient (patient 5) was advised to discontinue.

All 17 remaining patients completed the user-experience questionnaire. In general, patients were positive about the usability and acceptability of the device (Table 2). The majority reported that the device was easy to use and suitable for use at home. All patients preferred at home to in-clinic measurements of muscle strength. Patients were least positive about the ease of use when positioning their legs and the need for assistance from their caregiver. Caregivers assisted with positioning of the legs and storing the device after use. Areas for device improvement highlighted by patients were: (1) preventive measures for floor sliding,

Table 2. User-experience.

Survey items	Responses, *n* (%)		
	(Very) easy	*Neutral*	*(Very) difficult*
1. Taking a seat in front of the device was	10 (59)	3 (18)	4 (24)
2. Pressing the buttons was	15 (88)	0	2 (12)
3. Following the instructions on the device was	17 (100)	0	0
4. Performing the muscle strength measurement was	15 (88)	2 (12)	0
	(Totally) agree	*Neutral*	*(Totally) disagree*
5. I find the device user-friendly	14 (82)	1 (6)	2 (12)
6. I find the device suitable to measure muscle strength at home	17 (100)	0	0
7. I would like to monitor my muscle strength at home in the future	15 (88)	0	2 (12)
8. I am unsure about measuring muscle strength correctly in the absence of a healthcare professional	2 (12)	1 (6)	14 (82)
9. Measuring muscle strength at home is burdensome	4 (24)	0	13 (76)
10. I would rather measure my muscle strength at home than in the clinic	17 (100)	0	0
11. Measuring muscle strength every 2 (two) weeks is acceptable to me	16 (94)	0	1 (6)
12. Measuring muscle strength every 4 (four) weeks is acceptable to me	12 (71)	3 (18)	2 (12)
	Yes	*No*	
13. A caregiver helped me to perform the test*	9 (53)	8 (47)	

*Types of assistance were: Help with positioning the legs on the device ($n = 2$), help with pressing the buttons ($n = 2$), help with (un)storing the device ($n = 3$), a combination of these ($n = 2$).

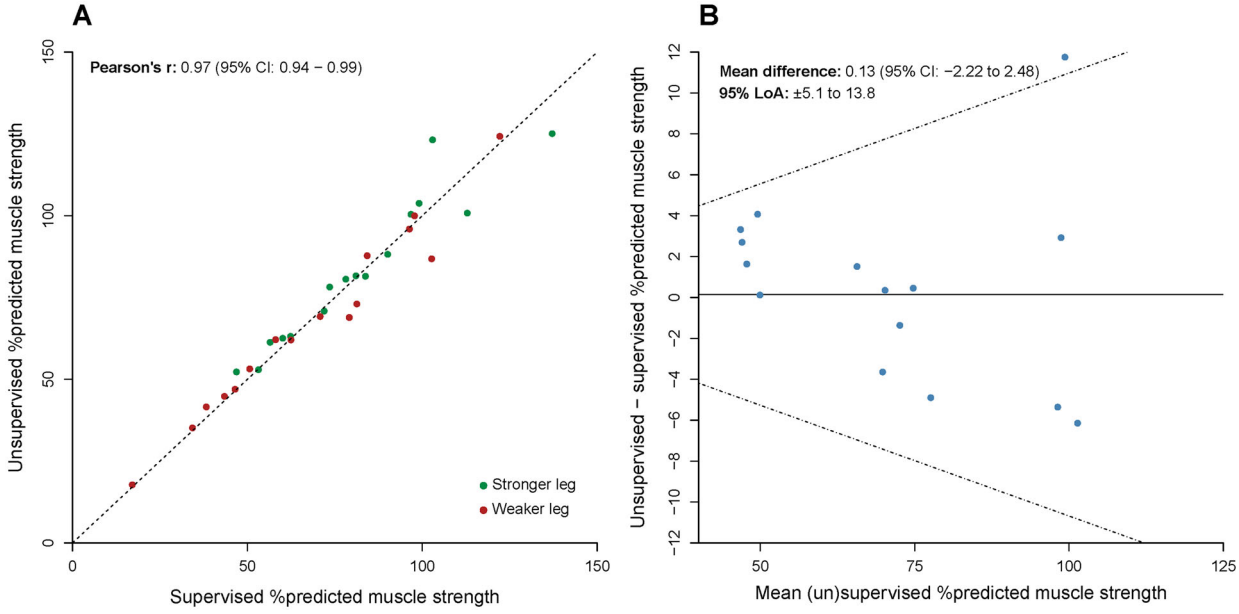

Figure 3. Reliability of the unsupervised versus supervised %predicted muscle strength scores. Unsupervised versus examiner-supervised %predicted muscle strength scores as measured by the PFD presented in a scatterplot (A) and in a Bland-Altman plot (B). Colors reflect the muscle strength scores of the stronger (green), weaker (red), and mean across legs (blue). Dotted line represents the identity line (A) or 95% limits of agreement (B). Abs. LoA: limits of agreement.

(2) tiltable shin plates for leg positioning and (3) ability to view PFD scores in a mobile app.

Reliability

The Pearson's *r* correlation coefficient, used to compare the unsupervised and supervised muscle strength scores, was 0.97 (95%CI: 0.94 – 0.99), indicating an excellent correlation (Figure 3(A)). The mean difference between unsupervised and supervised scores was 0.13 in %predicted muscle strength (95%CI; −2.22 – 2.48, $p = 0.91$) (Figure 3(B)). To compare unsupervised muscle strength scores over time, the ICC was calculated (Figure 4). During follow-up, test-retest reliability was excellent with an average ICC of 0.97 (95%CI: 0.94 – 0.99) and SEM of 5.8% (95%CI: 4.8 – 7.0). This means that 95% of the test–retest muscle strength values lay within ±11.4% of their observed value (i.e., ±1.96 times the SEM).

Sensitivity for detecting longitudinal change

Finally, the change in muscle strength over time per patient is illustrated in Figure 5. Muscle strength declined every month by an average of

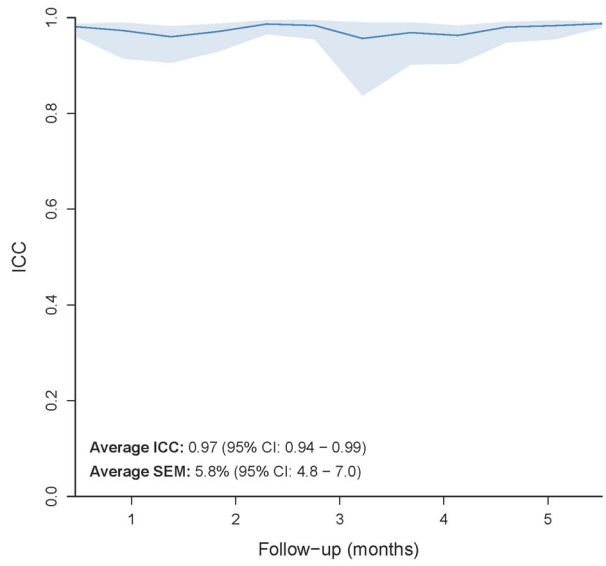

Figure 4. Test-retest reliability of the unsupervised %predicted muscle strength scores during follow-up. The intraclass correlation coefficient (ICC) was calculated over time comparing every two consecutive, unsupervised, mean %predicted muscle strength scores, as measured by the PFD. Abs. SEM: standard error of measurement.

2.5 points (95%CI; −3.9 to −1.0, $p = 0.002$) in the stronger leg, and 1.3 %predicted points (95%CI; −2.2 to −0.4, $p = 0.007$) in the weaker leg (Table 3). When both legs are taken into account, muscle strength declined by an average of 1.9 %predicted points (95%CI; −3.0 to −0.9, $p = 0.001$) every month. In contrast, the gross motor function domain of the ALSFRS-R worsened over time by 0.2 points per month (95%CI; −0.3 to −0.1, $p = 0.002$). Despite a Pearson's r correlation coefficient of 0.61 (95%CI: 0.18 − 0.84) in %predicted muscle strength between the stronger and weaker leg at baseline, the signal-to-noise ratio increases when averaging scores over both legs compared to using scores of only one leg. This indicates that differential progression may be detected more easily and measuring both legs is still more informative.

Discussion

In this study, we pilot our newly developed device to measure knee extension strength in the home setting. The device was well accepted by patients with ALS, and resulted in reliable and sensitive estimates of muscle strength, which adds to a variety of remote technological solutions to track different disease aspects of ALS (26,35,36). This builds toward a holistic, decentralized assessment of patients, which not only has significant value for patients, by reducing the burden and expanding their access to research and care, but also for healthcare professionals, by deepening the available information required for adequate medical decision-making.

Progressive loss of muscle strength is regarded as the hallmark of disease progression in ALS and is reported by patients, together with respiratory function, as the most important outcome for home-monitoring (24). The severity of muscle weakness influences the ability to perform activities of daily living, making it a crucial outcome for assessing disease progression and detecting (early) treatment responses of new therapeutic interventions. The importance of muscle strength in the search for new effective therapies (6,7,37), and the current shift toward remote monitoring (24,25), stress the need for methods that allow unsupervised home-based assessment of muscle strength. Home-based assessment of muscle strength may alleviate travel burden for patients and reduce the burden of participating in clinical trials, while providing a more complete understanding of patient functioning in daily life. With a view to care, remote monitoring of muscle strength may aid the facilitation of personalized visit schemes to reduce travel burden (30,38), increase access to multidisciplinary care, and improve quality of life (39,40).

We found that the unsupervised and supervised measurements were highly correlated and that there was no systematic difference between them. During follow-up, the measurement error between consecutive unsupervised measurements was minimal. This indicates that for most patients, a single training session was sufficient for them to perform reliable unsupervised measurements. Interestingly, the average standard error of measurement between unsupervised measurements was 5.8%, which is comparable to supervised measurements performed on similar devices (range: 6.2–8.9%) (11,12,14). Furthermore, our signal-to-noise ratios suggest that averaging muscle strength scores across both legs is more sensitive in detecting longitudinal change compared to scores of individual legs. This might be explained by correlated muscle strength loss between legs over time, thereby increasing the signal when legs are combined (41,42).

Our study does have limitations. Although the design offers important insight into the feasibility and reliability of remote muscle strength measurements, the limited sample size and inclusion of slowly progressive patients prevents a thorough examination of long-term progression, the association with key clinical parameters and generalizability to faster progressing ALS populations. Current results were, therefore, unable to determine the natural progression of muscle strength during typical trial durations when measured by home-based devices, to identify possible differences between subgroups (e.g. site of disease onset, wheelchair use), or to compare these findings to other traditional outcomes. Furthermore, it remains to be established how remote monitoring

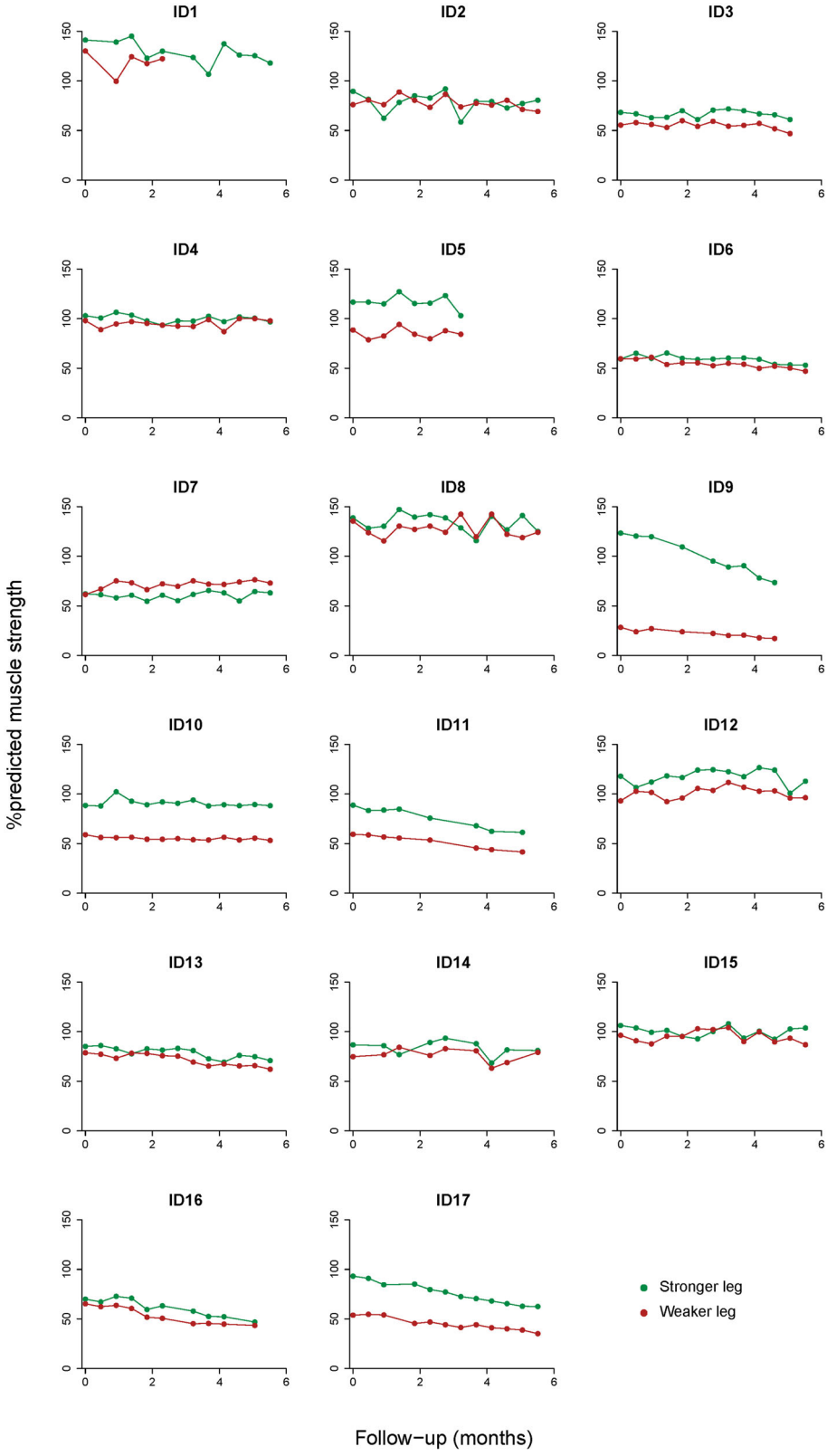

Figure 5. Longitudinal change in muscle strength per patient. Spaghetti plots of the individual %predicted muscle strength scores during follow-up as measured by the PFD. Muscle strength scores of the stronger and weaker leg are color-coded in green and red, respectively.

benefits, such as increased sampling frequencies, might decrease within-patient variability and thereby lower required sample sizes (25). These considerations should be addressed to optimize signal-to-noise ratios and to inform optimal protocol design. Nevertheless, home-based assessment of muscle strength provides a unique perspective on daily functioning of patients outside the clinic. To enable widespread adoption, the device should subsequently be evaluated in wider

Table 3. Longitudinal rates of decline during follow-up.

	Intercept	Slope (*SD*)*	*p* Value	Between-variability	Within-variability	Signal-to-noise ratio
%**predicted strength**						
Mean	86.7	−1.9 (0.5)	0.001	2.0	5.6	0.95
Stronger leg	96.1	−2.5 (0.7)	0.002	2.8	5.8	0.89
Weaker leg	77.2	−1.3 (0.4)	0.007	1.5	4.9	0.85
ALSFRS-R						
Total score	37.7	−0.7 (0.2)	0.003	0.8	1.0	0.82
Bulbar subdomain	10.6	−0.2 (0.1)	0.085	0.5	0.5	0.44
Fine subdomain	8.2	−0.2 (0.1)	0.006	0.3	0.5	0.80
Gross subdomain	8.9	−0.2 (0.1)	0.002	0.2	0.5	0.99
Respiratory subdomain	10.0	−0.0 (0.1)	0.54	0.2	0.6	0.17

Abs. ALSFRS-R: ALS functional rating scale.
*Mean monthly rate of change.

populations by implementing remote monitoring of muscle strength as an exploratory endpoint in larger studies. Our findings show that measuring muscle strength at home can be difficult and burdensome for some patients. Consequently, patients require assistance from a caregiver, potentially increasing caregiver burden and reducing long-term adherence. During this study, several suggestions were made to further improve the device in order to fully utilize the potential of home-monitoring. Currently, the device only measures one muscle group and might, therefore, not completely capture gross motor function loss. To increase the number of muscle groups, muscle strength measurements could be supplemented with e.g. remote collection of hand grip dynamometry or accelerometry (26,43–45). Extensive muscle testing is time-consuming, however, and leads to fatigue and increased patient burden, resulting in inaccurate measurements and attrition over time (2,46). It is therefore desirable to perform a minimum number of assessments, while generating sufficient information for monitoring muscle strength loss. Muscle groups with a long measurement horizon over the course of the disease, like the quadriceps, may be preferred over muscle groups that become fully paralytic early in the disease (42). Efforts are needed to define the optimal set of measurements that minimize patient burden, while generating sufficient information about disease progression. In addition, giving extra weight to dominant side muscle strength loss may further improve the measurement strategy and potentially better relate muscle weakness to the impact on the patient's daily life.

In conclusion, our newly developed device showed to be feasible in patients with ALS to perform knee extension strength measurements at home. The device produces reliable results and is sufficiently sensitive to detect differential muscle strength loss. This study reveals the potential of remote monitoring of muscle strength to capture disease progression in patients with ALS, and may facilitate a more patient-centric clinical trial and care model. Larger studies are warranted to compare the device with conventional outcomes in order to determine long-term adherence and muscle strength progression.

Acknowledgments

The authors would like to thank Brenda Vollers-King for assistance with language editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study was supported by Stichting ALS Nederland under Grant 2018-0009.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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