New accelerometer-based biomarkers to track disease progression in amyotrophic lateral sclerosis

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Abstract

Background ALS is a progressive neurodegenerative disease that is incapacitating and obstruct patients to participate in clinical trials. The most commonly used method to assess functional decline in ALS is the ALSFRS-R scores. Due to their subjective nature, there is need for a more objective way to quantify the disease progression. Remote monitoring can help objectively quantify the progress of ALS while simultaneously lower the burden to participate in clinical trials and enhance the understanding of ALS.

Methods Based on the activity index metric, three new accelerometer-based biomarkers were developed to capture either the physical activity, physical capacity, or total physical functioning of patients with ALS. The progression of the disease was then assessed using multiple linear mixed estimator models with different thresholds. Additionally, the outcomes of the biomarkers were evaluated on how they relate to the ALSFRS-R scores.

Results The three biomarkers all show a (strong) significant declining trend over time with progression of the disease. On average the physical activity declined monthly with 0.98% [p-value=0.012], the physical capacity with 2.16% [p-value<0.001], and the total physical functioning with 2.84% [p-value <0.001] compared to data at baseline. Physical capacity and total physical functioning showed a moderate to strong positive correlation with various ALSFRS-R scores [r 0.49 – 0.65].

Conclusion The findings suggest that the activity index is a suitable instrument to quantify the functional decline of ALS patients, and that biomarkers significantly reflect the functional decline in ALSFRS-R scores. Future research is necessary to improve the quantification of ALS and thus enhance therapeutic trial.

Keywords *ALS · ALSFRS-R · Remote monitoring · Activity Index · Biomarkers*

Introduction

Approximately every 90 minutes one patient is diagnosed with Amyotrophic Lateral Sclerosis [ALS]. This is an incurable neurodegenerative disease, with a median survival of three to five years, that affects both the brain and nervous system [14]. Subacute combined degeneration of the spinal cord causes death of motor neurons between the spinal cord and the brain. This will eventually culminate in the loss of muscle control. Patients diagnosed with ALS encounter gradual trouble with voluntary movement such as walking or grasping of objects with their hands. Alternatively, some patients lose control of speaking, swallowing and even breathing. Eventually leading to a patient's death [17].

Many scientists attempt to comprehend the complexities and progression of ALS. A source of concern is the wide range of patient differences [i.e., patient heterogeneity]. Because of the presence of various neuropathological and hereditary aspects of the disease, the progression of ALS varies greatly among patients [17]. Clinical trials are routinely used to track the progression of ALS patients' physical activity, respiratory failure, spirometry, dietary status, phenotypic, and other environmental factors to find new treatments [9]. In addition, patients, frequently find it difficult to participate in research trials due to the nature of this merciless incapacitating disease [4]. Even if attendance is possible at the start, some patients will not be able to complete the clinical trial [6]. The ALS

Functional Rating Scale [ALSFRS-R] is the most commonly used method for tracking functional decline in ALS. This is a subjective method that demonstrates how a patient progresses over time based on a questionnaire score given by patients. The need for an objective measure can be powerful to evaluate the efficacy in understanding the progression of ALS [18]. The use of remote digital health technologies [e.g., accelerometer-based data] is a relatively new yet promising strategy to objectively research the progression of ALS [15,16]. This strategy uses a remote device, such as the Actigraphy, that a patient has to wear either on the wrist or the hip to remotely monitor the movement patterns to track the progression of the disease. This strategy lowers the entry barrier for patients to participate in and complete these clinical studies and has the potential to improve the understanding of how ALS progresses between patients and the ability to detect new treatment effects. In contrast to the Activity Counts [AC] used by van Eijk et al., [2019], this study will employ a new accelerometer-based metric. The Activity Index [AI] proposed by Bai et al., [2016] captures movement patterns and can be computed using actigraphy device data. The AI is preferred over other accelerometer-based outcomes used in previous studies [3,8,16], such as the Euclidean Norm Minos One [ENMO] and Activity Counts [AC]. This is primarily due to the increased transparency and additivity, as well as rotational invariance in the AI [3]. As a result, this metric is better at distinguishing [i.e., predicting] between sedentary and non-sedentary activity. Only a few researchers have investigated the relationship between accelerometer-based biomarkers and the ALS progression [16]. The primary goal of this study is to incorporate the remote digital health strategy and to investigate how ALS progresses over time using new accelerometer-based biomarkers that capture physical activity and physical capacity. In addition, it will investigate how these new biomarkers are correlated with ALSFRS-R scores. It is important to extent the scarcity of literature because neurologists now mainly rely on clinical criteria for prognosis. New accelerometer-based biomarkers can assess the progression of ALS in an objective way and therefore has great potential to improve therapeutic trial while simultaneously lower trial costs, maximize information collection and lower the burden for patients [9,16].

Methods

Study Sample

This study has access to the data of 42 Dutch patients with a motor neuron disease [e.g., ALS] previously used in the research paper by van Eijk et al. [2019]. The patients were approached through the medium of a Dutch web-based patient registry [TRICALS] and were eligible to participate in the trial when they suffered from a motor neuron disease. Table 1 illustrates the characteristics of the patients that participated in the study.

Ethical Considerations

The patients in this study volunteered to take part. Each of them was approached individually to provide informed consent about the purpose of this study and the findings. As a result, it was approved by the UMCU's Medical Ethics Committee. Finally, the authors of the study by van Eijk et al. [2019] de-identified the patients from the dataset to maintain anonymity of participants.

Accelerometer Data and accelerometer-based outcomes

The raw accelerometer data was collected with the Actigraph Link GT9X. The 42 participants were asked to wear the Actigraphy on the right hip in the anterior axillary line. The participants had to wear this device for 7 consecutive days during waking hours and a maximum follow-up of 18 months with intervals of 2-3 months. The Actigraphy accelerometer is a small and lightweight device that tracks tri-axial accelerations of the participant wearing it and is measuring their cycles of activity. The tri-axial accelerations are measured in x, y, and z value which respectively correspond to vertical, forward, and sideway movements. The values are measured in gravitational units with a dynamic range of approximately ± 8g [$1g = 9{,}81\, m * s^2$].

Table 1 *illustrates the baseline characteristics of the 42 patients at baseline. MND stands for motor neuron disease.*

Characteristics	Overall (n = 42)
Age, mean (SD), (*years*)	60 (12)
Manes, no. (%)	31 (74)
MND Subtype, no. (%)	
ALS	39 (93)
PMA	3 (7)
PLS	0 (0)
Bulbar onset, no. (%)	7 (17)
Symptom duration (months)	
Median	25
Range	7-218
Diagnostic delay (months)	
Median	8
Range	2-130
Riluzole use, no. (%)	30 (71)
Body mass index, mean (SD), (kg/m^2)	25 (3)
ALSFRS-R total score, mean (SD)	36 (8)
Prognostic subgroup, no. (%)	
Very long	16 (38)
Long	14 (33)
Intermediate	11 (26)
Short	1 (2)
Very short	0 (0)

The raw accelerometer data was processed using R studio [version 3.4.1], which was then summarized using the Summarized Actigraphy package. Each patient's datafiles were examined and non-wear time periods were removed. The sample rate was set to 30 Hertz [Hz], indicating that each second contains 30 observations [i.e., each full day of wearing the device contains 2.592.000 datapoints per tri-axial directions]. Because of the size of these large data sets per patient, each 30 observations per second were first reduced to 1 observation per second [i.e., epochs of 1s.] and then an average of 1 observation per minute [i.e., epochs of 60s.] was taken for one day. This means that each patient's baseline and follow-up data was reduced to 1440 measurements per day on average.

The Summarized Actigraphy package uses the Activity Index [AI] by Bai et al. [2016] to summarize the data of each patient. The AI is expressed with the following formal notation; $AI_i^{ABS}(t;H) = \sqrt{\max\left(\frac{1}{3}\left\{\sum_{m=1}^{3}\sigma_{im}^2(t;H) - \bar{\sigma}_i^2\right),\ 0\right\}}$ and calculates the standard deviation of the variances of the vector magnitudes minus the noise around those variances [3]. Three different outcomes were computed to summarize the physical activity or physical capacity in one single value [i.e., the 1440 measurements per day per person per follow-up were reduced to 1 measurement]. The physical activity measures how active a patient is during the day and the physical capacity measures how capable patients are to make strong movements. (1) Measure for physical activity: Proportion Active [hereafter, PA]; (2) Measure for physical capacity: Variation of Movement [Hereafter, VM]; and (3) measure for total physical function; the Composite Model [Hereafter, CM]. The PA (1) is calculated conditional on a threshold for AI values. When a patient's AI value exceeds a certain threshold, it is considered activity during the day. Thresholds were made for AI values of 0.1, 0.25, 0.5, 0.75, and 1.0. This means that a patient can have a proportion between 0.0 and 1.0 [i.e., 0.0% or 100.0% active during the day]. It was hypothesized that as the disease progresses, patients would move less during follow-ups and thus would be less likely to exceed this threshold, resulting in a lower PA during a day. The VM (2) is calculated as the standard deviation of the AI, when the value of the AI exceeds the threshold used for the PA [i.e., if the PA is based on the threshold of 0.5, the standard deviation of the AI is only measured over the range of values of AI > 0.5]. Additionally, the VM was also winsorized for the 99 percent quantile to exclude extreme values [5]. It was hypothesized that the VM has a power of explaining how strong movements are changing [i.e., when the standard deviation of the AI is high it implies that the patient is capable of making strong movement changes]. The CM (3) is calculated as the PA (1) x the VM

(2). It was hypothesized that this would reflect the total change for both physical activity and physical capacity per patient [i.e., total physical functioning].

Statistical Analysis

This study quantifies the disease progression of ALS by means of physical activity and physical capacity markers based on the activity index metric using a sample of 42 Dutch patients who participated in a longitudinal cohort study between 7-10-2016 and 1-11-2018. This progression was assessed with multiple linear mixed estimator models [LME] with the following thresholds: 0.1, 0.25, 0.5, 0.75, and 1.0. Linear mixed models assume a hierarchical data structure in which data points are grouped. This is a popular method in longitudinal cohort studies mainly because the models can make a distinction between clusters of groups and therefore account for the correlation structure [in this case, a distinction between all the patients individually per time]. Therefore, this study incorporates linear mixed models fitted with a fixed effect for time and a random intercept and slope for time per individual. This is expressed in the following formal notation; $A_{ij} = \gamma_{00} + u_{0j} + (\gamma_{11} + u_{1j})\, time_{ij} + e_{ij}$, where A_{ij} is one of the three accelerometer-based biomarkers, $u_{0j}\ and\ u_{1j}$ represent the individual parameters for the intercept and the slope, respectively. The parameter for the fixed intercept [γ_{00}] describes the average physical activity or capacity data point at baseline [i.e., how physically active, or physically capable patients are in the beginning] and the parameter for the fixed slope [γ_{11}] describes the longitudinal monthly rates of change in physical activity or physical capacity [i.e., the average monthly progression of the disease]. The signal to noise ratio was calculated to assess between-patient variability. This is calculated as the standard deviation of the slope [i.e., random effect of time] divided by monthly mean rate of change $\left[\frac{\sigma_{u1}^2}{\gamma_{11}}\right]$ [16]. A lower signal to noise ratio indicates a more accurate model and less variation between patients [i.e., improved disease progression detection] [16]. Furthermore, the CM assumes to capture both the variance and error of the physical activity and the physical capacity which increases the uncertainty of the model. As a result, the lowest signal to noise ratio was more important than the fastest percentual monthly decline on average. In addition, the correlation between three accelerometer-based outcomes and ALSFRS-R questions are studied. The ALSFRS-R is a mechanism for tracking disease progression based on a point-based questionnaire that patients must complete at each follow-up. The LME were computed either using de nmle and lme4 package in R studio.

Results

Longitudinal rates of change

The results of the linear mixed models are given in Table 2. The outcomes of the various thresholds illustrate a lot of variation among the data at baseline and their monthly rates of decline for each model. Based on the VM [physical capacity], patients on average do have a baseline value between 0.969 and 0.983 and longitudinal monthly rates of decline between 0.021 and 0.022 [all p-values < 0.001]. This implies that for a given patient and a given month, on average a patients' VM declines between 2.15% and 2.22% compared to data at baseline and conditional on their threshold. Consequently, this means a decline of physical capacity of approximately 38% to 40% over 18 months compared to data at baseline. Furthermore, based on the PA [physical activity] at baseline, patients were on average 32.0% to 74.4% active and had a monthly rate of decline between 0.5% and 0.8% [all p-values < 0.05], conditional on the threshold. This implies that for a given patient and a given month, on average the percentage a patient was active declined between 0.72% and 2.43% compared to data at baseline and conditional on their threshold. Consequently, this means a decline of physical activity of approximately 13% to 44% over 18 months compared to data at baseline. Finally, the CM [total physical functioning] exhibits an even steeper decline in longitudinal monthly rates. On baseline data, patients start on average with

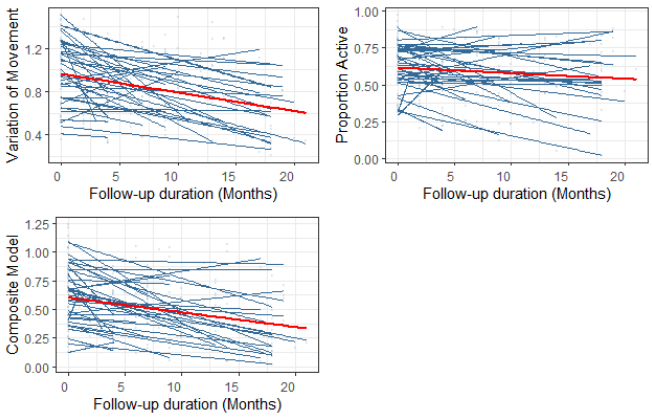
Table 2 *exhibits the LME models for three different accelerometer-based outcomes and their corresponding threshold [0.1,0.2,0.5,0.75, and 1.0]. The table further illustrates the intercept [that is, data at baseline], the slope [that is, the monthly rates of change during follow ups], the 95% Confidence interval and p-values for the slopes and lastly the signal to noise ratio. The signal to noise ratio is calculated as the standard deviation of the slope divided by monthly mean rate of change* $\left[\frac{\sigma_{u1}^2}{\gamma_{11}}\right]$ *and indicates how accurately disease progression can be detected.*

Outcome Variable		*Model Parameters*				Signal to noise ratio
		Intercept	Slope	95% CI	*p* values	
Threshold	*0.10*					
Variation of Movement		0.969	-0.021	-0.028 to -0.014	**<0.001**	-0.65
Proportion Active		0.744	-0.005	-0.010 to -0.001	**0.024**	-1.72
Composite Model		0.718	-0.019	-0.026 to -0.012	**<0.001**	-0.77
Threshold	*0.25*					
Variation of Movement		0.978	-0.021	-0.028 to -0.014	**<0.001**	-0.61
Proportion Active		0.618	-0.006	-0.011 to -0.001	**0.012**	-1.63
Composite Model		0.609	-0.017	-0.024 to -0.011	**<0.001**	-0.76
Threshold	*0.50*					
Variation of Movement		0.983	-0.022	-0.028 to -0.015	**<0.001**	-0.51
Proportion Active		0.474	-0.006	-0.011 to -0.002	**0.006**	-1.60
Composite Model		0.480	-0.014	-0.020 to -0.009	**<0.001**	-0.83
Threshold	*0.75*					
Variation of Movement		0.979	-0.022	-0.028 to -0.015	**<0.001**	-0.42
Proportion Active		0.386	-0.008	-0.012 to -0.003	**0.001**	-1.28
Composite Model		0.394	-0.013	-0.018 to -0.008	**<0.001**	-0.86
Threshold	*1.0*					
Variation of Movement		0.971	-0.022	-0.028 to -0.015	**<0.001**	-0.30
Proportion Active		0.320	-0.008	-0.012 to -0.004	**<0.001**	-1.09
Composite Model		0.328	-0.012	-0.017 to -0.006	**<0.001**	-0.94

an intercept between 0.328 and 0.718 and have a monthly rate of decline between 0.012 and 0.019 [all p-values < 0.001]. This implies that for a given patient and a given month, on average a patient declines between 2.69% and 3.53% conditional on their threshold. Consequently, this means a decline of the total physical functioning of approximately 48% to 64% over 18 months compared to data at baseline. The accuracy of the model was assessed by means of the signal to noise ratio. The signal to noise ratio shows the between-patient variability [i.e., presence of slow- and fast progression in patient]. The results in Table 2 indicate that the signal to noise ratio for the VM and the CM is considerably lower than for the PA. Conditional on the threshold, the signal to noise ratio improves from respectively, -0.65 to -0.30 for VM and -1.72 to -1.09 for PA. The signal to noise ratio for the CM first improves from -0.77 to -0.76 and then deteriorates to -0.94.

Figure 1 illustrates the three biomarkers over time based on the best signal to noise ratio for the CM. This corresponds with a threshold of 0.25. The figure illustrates the average intercept and slope for the patients [red line] and the random intercept and slope per patient for each follow-up [blue line]. The red line implies that on average patients' decline monthly over time. On the other hand, the blue lines illustrate the between patient variability. On average, the physical activity, physical capacity, and total physical functioning of each patient individually declines over time. However, it is well visualized that among these patients there is a lot of variation for the data at baseline as well as for the progression of the disease. This means that there is a lot of disparity between the start of, and decline in physical activity, physical capacity, and total physical functioning between patients.

Fig 1. *Exhibits the three biomarkers with the follow-up months. The red line shows the fixed intercept and fixed slope for the data at baseline and the longitudinal monthly rates of decline for the average patient. The blue lines show the random intercept and random slope – individually per patient – for the data at baseline and the longitudinal monthly rates of decline. The biomarkers correspond to a threshold of 0.25 with the lowest signal-to-noise-ratio for the composite-model*



Correlation with disease progression

Figure 2 illustrates a boxplot between the different accelerometer-based biomarkers and question 8 of the ALSFRS-R score [left 3 boxplots]. The accelerometer-based biomarkers were based on a threshold of 0.25 with the lowest signal to noise ratio for the CM. Question 8 specifically relates to the walking ability of patients. The scores on the horizontal axis range from 0 [bad] to 4 [good] and indicate how well a patient is able to walk. The results point out that the VM as well as the CM are moderate to strong positively correlated with the walkability among patients [r 0.54; 95% CI 0.43-0.75, p<0.001]. Additionally, the mean VM and the CM illustrate a strong linear trend in levels of walking with mean levels per score of respectively, 0.38, 0.54, 0.81, 0.97, and 1.08 for the mean VM and 0.17, 0.22, 0.50, 0.55, and 0.77 for the CM. This implies that on average a higher value as a measure of physical activity or total physical functioning is associated with patients that specified being able to walk. Moreover, the PA is also positively correlated with walkability but is a lot lower compared to the other accelerometer-based biomarkers [*r 0.32; 95%* CI 0.20-0.44, *p*=0.022]. Also, the PA illustrates a less linear trend in levels of walking with mean levels per score of respectively, 0.47, 0.41, 0.61, 0.57, and 0.72. Figure 2 also illustrates the correlation between the different accelerometer-based outcomes and question 4 of the ALSFRS-R score [right three boxplots]. Question 4 specifically relates to the ability of patients to write. The scores on the horizontal axis range from 0 [bad] to 4 [good] and imply how well a patient is able to write. The results illustrate that the VM, the PA and the CM are only slightly correlated with the writing ability of patients [*r 0.19; 95%* CI 0.057-0.32, *p*<0.001, *r 0.29; 95%* CI 0.16-0.41, *p*=0.019, and *r 0.26; 95%* CI 0.13-0.39, *p*<0.001]. Additionally, mean VM and the CM show less linear trend in levels of walking with mean levels per score of respectively, 0.71, 0.91, 0.72, 0.83, and 0.94 for the mean VM and 0.33, 0.55, 0.49, 0.49, and 0.61 for the CM. This implies that on average a higher value as a measure of physical activity and physical capacity is not strongly associated with patients that specified being able to write.

Figure 3 illustrates the correlation between the different accelerometer-based outcomes and the gross motor skill questions [Q8,9,10] of the ALSFRS-R score. The gross motor skill questions specifically relate to the ability of patients to use large muscles in the arms, legs, and torso. The scores on the horizontal axis range from 0 [bad] to 12 [good] and indicate how well a patient is able to utilize big muscle movements. The results illustrate that the VM, the PA and the CM are moderate to strong positively correlated with gross motor skill of patients [*r 0.62; 95%* CI 0.53-0.70, *p*<0.001, *r 0.41; 95%* CI 0.29-0.52, *p*=0.004, and *r 0.65; 95%* CI 0.56-0.72, *p*<0.001]. This implies that on average a higher value as a measure of physical activity, physical capacity and total physical functioning is positively associated with patients being able to utilize their gross motor skills.

Finally, Table 3 summarizes the relationship between the three different accelerometer-based outcomes and question-specific

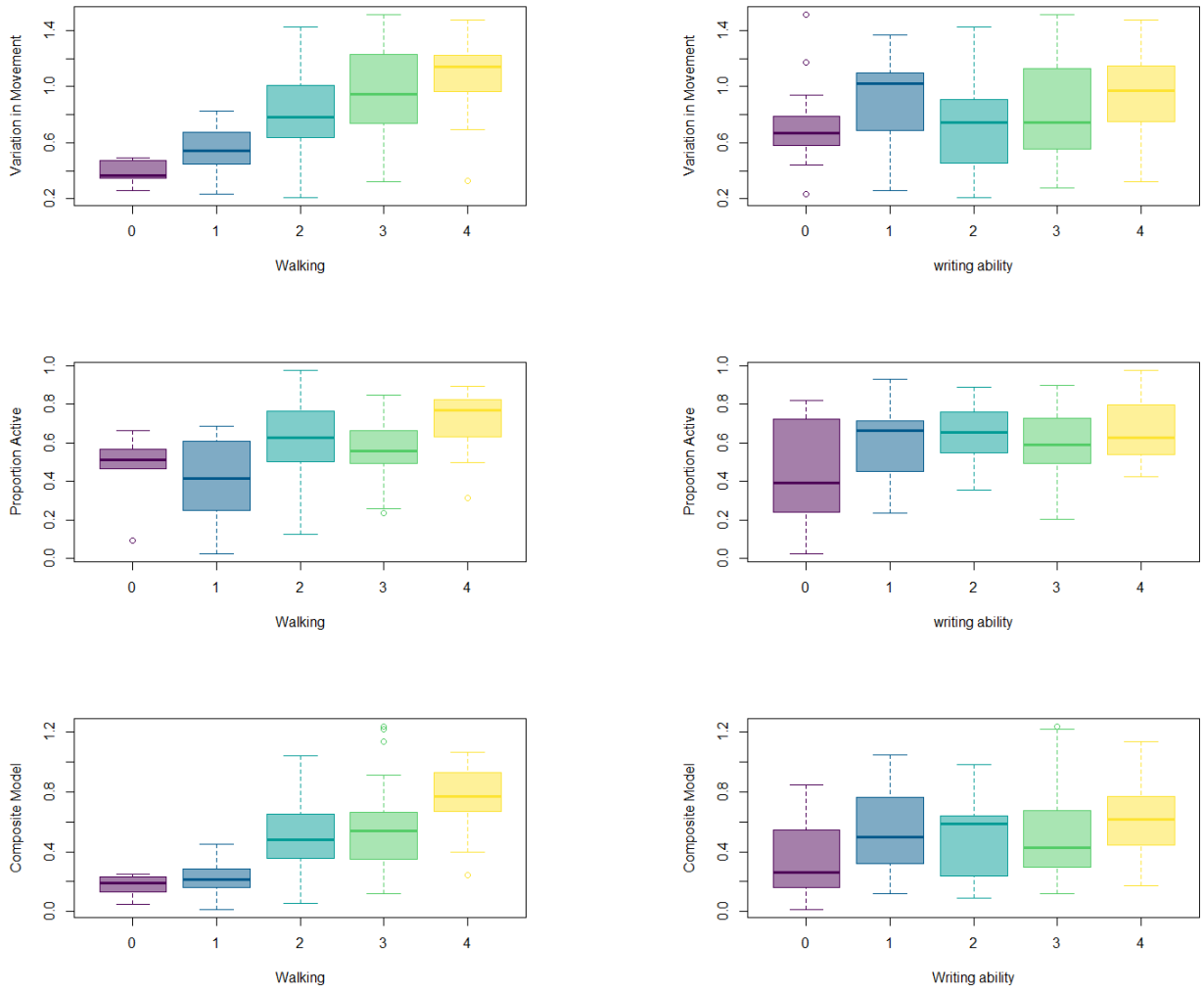


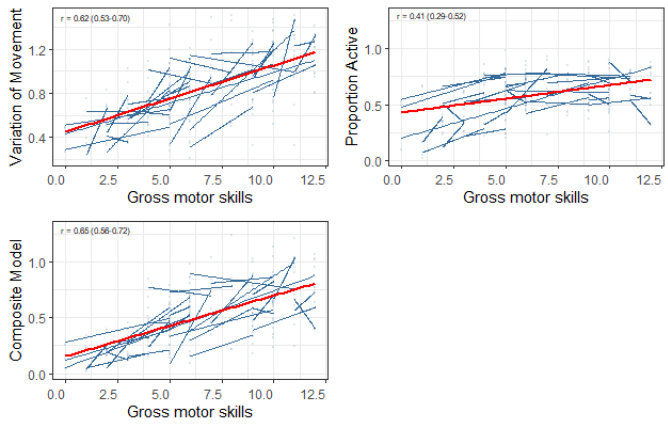
Fig 2. *Illustrates boxplots for the three biomarkers versus ALSFRS-R question related to walking (the three boxplots on the left; Q8) and the ALSFRS-R question related to writing (the three boxplots on the right; Q4).*

Discussion

ALSFRS-R scores namely, gross motor skills [Q8,9,10], walkability [Q8], total score [all questions], and ability to write [Q4] for all thresholds. The results indicate that with each step increase in threshold, the correlation between VM and all question specific ALSFRS-scores decreases. Conversely, the correlation between the PA and the ALSFRS-R scores illustrates an increasing trend with each step increase in threshold. Finally, increasing the threshold has little to no effect on the correlation between the CM and ALSFRS scores.

This study attempted to determine the extent to which three new accelerometer-based biomarkers can reflect disease progression of patients with ALS. The LME results for the three accelerometer-based biomarkers exhibit a surprising range of outcomes. The VM shows an average monthly decline of 2.15% to 2.22% of physical capacity per threshold compared to data at baseline [38-40% over a timeframe of 18 months]. This means that as the threshold is raised, the AI's standard deviation remains unchanged. This is assumable

Fig 3. *Exhibits the correlation between the three biomarkers with the Gross motor skills [ALSFRS-R Q7,8,9]. The red line shows the fixed intercept and fixed slope for the data at baseline and change in gross motor skill score. The blue lines show the random intercept and random slope – individually per patient – for the data at baseline and change in gross motor skill score. The biomarkers correspond to a threshold of 0.25 with the lowest signal-to-noise-ratio for the composite-model*



because VM should not depend on non-movement thresholds but rather on variations in large movements. The PA illustrates an increasing monthly decline of physical capacity of 0.72% to 2.43% per threshold compared to the data at baseline [13-44% over timeframe of 18 months]. Presumably, because each increase in threshold lowers the proportion that exceeds the threshold. This suggests that on average, patients tend to constantly fast decline in physical capacity [i.e., movements will look the same] but that on average patients tend to slowly decline in physical activity [i.e., being active or not being not active]. The progression of these biomarkers show that over time patients will faster decline in not make strong gross motor skill movements [physical capacity] but will much slower stop with doing nothing, conditional on the threshold [physical activity].

In addition, the CM assumes to capture the total physical functioning of patients. The results indicate that conditional on the threshold, the total physical function of patients decline on average between 2.69% and 3.53%, compared to data at baseline. As a result, the CM has the steepest slope. Based on the lowest signal-to-noise ratio, patients will be unable to perform more than half of their total physical functional movements [Monthly: -2.84%, 18 Months: -51%] on average after 18 months.

Furthermore, the three accelerometer-based biomarkers with a threshold of 0.25 had a moderate to strong correlation with gross motor skills or walking. The results show that the VM and the CM have a much stronger correlation compared to the PA. Assumedly, gross motor skills or walking rely on greater VM [physical capacity] and less on the PA [physical activity]. The PA does not indicate what a person is capable of, but rather how active a person is on an average day. Similarly, the correlation between VM and the CM is weakening for writing, while the correlation between the PA is not changing significantly. This is also assumed because writing has no effect on the AI's standard deviation because it is not a large change in movement.

Moreover, the various thresholds have only a minor effect on the correlations between the CM and the various (non)-gross motor skills. This is most likely due to the fact that the correlation decreases with VM and increases with PA. It is likely that the PA will have a higher correlation because the thresholds cause the slopes of the PA in the LME to increase and are thus more related to the decline in ALSFRS-R scores over time.

Nevertheless, this study is also subject to several limitations. To begin with, the ALSFRS-R scores are subject to subjectivity [18]. Patients are either examined by a neurologist, a scientist or it is self-reported [2,4,13]. As a result, these scores are vulnerable to professionals' ability to assess patients' perceptions of how the disease progresses. This may result in low [interobserver] reliability and as a result, a different outcome [i.e., correlation] between the ALSFRS-R score and the various biomarkers [2]. Also, because of the subjective nature of the ALSFRS-R score, it is then unclear whether the outcomes truly measure what you

Table 3 *exhibits the change of correlation coefficients of each biomarker conditional on their threshold between ALSFRS-R score of gross motor skills [Q7,8,9], walking [Q8], total score [all questions], writing [Q4]. Confidence intervals are between brackets.*

Correlation coefficient ρ and 95% CI

Variation of Movement	**Gross motor**	**Walking**	**Total score**	**Writing**
0.1	0.65 [0.56, 0.72]	0.55 [0.44, 0.64]	0.53 [0.42, 0.62]	0.24 [0.11, 0.37]
0.25	0.62 [0.53, 0.70]	0.54 [0.43, 0.63]	0.49 [0.38, 0.59]	0.19 [0.06, 0.32]
0.5	0.57 [0.47, 0.66]	0.51 [0.40, 0.60]	0.45 [0.33, 0.55]	0.16 [0.02, 0.29]
0.75	0.52 [0.42, 0.62]	0.47 [0.36, 0.57]	0.41 [0.29, 0.52]	0.13 [-0.00, 0.27]
1.0	0.49 [0.38, 0.59]	0.44 [0.31, 0.55]	0.40 [0.28, 0.51]	0.14 [0.00, 0.27]
Proportion Active				
0.1	0.25 [0.11, 0.37]	0.18 [0.05, 0.31]	0.34 [0.21, 0.45]	0.22 [0.09, 0.35]
0.25	0.41 [0.29, 0.52]	0.32 [0.20, 0.44]	0.46 [0.34, 0.56]	0.29 [0.16, 0.41]
0.5	0.60 [0.50, 0.68]	0.49 [0.38, 0.59]	0.55 [0.45, 0.64]	0.33 [0.20, 0.45]
0.75	0.67 [0.59, 0.74]	0.56 [0.46, 0.65]	0.58 [0.48, 0.66]	0.34 [0.21, 0.46]
1.0	0.69 [0.61, 0.76]	0.57 [0.47, 0.66]	0.57 [0.47, 0.66]	0.33 [0.21, 0.45]
Composite Model				
0.1	0.64 [0.55, 0.72]	0.54 [0.43, 0.63]	0.56 [0.45, 0.64]	0.26 [0.13, 0.39]
0.25	0.65 [0.56, 0.72]	0.54 [0.43, 0.63]	0.55 [0.45, 0.64]	0.26 [0.13, 0.39]
0.5	0.67 [0.59, 0.74]	0.56 [0.46, 0.65]	0.55 [0.45, 0.64]	0.27 [0.14, 0.39]
0.75	0.69 [0.61, 0.76]	0.58 [0.48, 0.67]	0.54 [0.44, 0.63]	0.27 [0.14, 0.40]
1.0	0.69 [0.61, 0.75]	0.58 [0.48, 0.67]	0.53 [0.42, 0.62]	0.27 [0.14, 0.40]

want to know, either physical activity or physical capacity. Alternatively, there could be some flaws in the data [processing]. The actigraphy was sent by mail and patients were asked to wear it for 7 consecutive days during waking hours. Data visualization revealed that a few [two] patients had a strong upward trend in their daily biomarkers over time. Physical improvement is not possible due to the disease's progressive nature [1]. Presumably, these two patients [and possibly others, where it was not as obvious as with these patients] wore the actigraphy during interrupted times of the day [e.g., when going for a walk or other non-sedentary movement] or patients were able to move but chose to not to in the beginning of the study. Also, due to the extent of the raw data, which contained millions of observations per patient, each dataset was reduced to 1440 observations per patient per follow-up [i.e., 1440 observations of 1 minute = 1 average day]. As a result, missing values that were averaged over other days were overlooked, potentially leading to incorrect movement measurements. Either incorrect data or incorrect data processing could result in a slight distortion of the biomarker computation and, therefore, biased LME outcomes and a false correlation or signal to noise ratio.

Future research is required to improve the validity and reliability of the data as well as the outcomes of the biomarkers. Additional questions on the ALSFRS-R could be added to make a more appropriate distinction between movements in physical activity and physical capacity. This increases the likelihood that the biomarkers will actually reflect what they are measuring. Second, the biomarkers could be fine-tuned to improve model outcomes and tested against other accelerometer-based markers to ensure the accuracy of the results. Finally, to ensure the quality of the data, the design of study can be changed. The accelerometer should be worn for a longer period of time [e.g., 5 days for 4 weeks every 2-3 months]. Only wearing it for 7 days increases the possibility that environmental, social[-economic], or personal factors played a role in a patient's inability to move even though the patient was able to make movements [e.g., weather, or other health issues] [7,11].

To conclude, this study showed how various new biomarkers quantitatively reflect the progression of ALS and how they relate to the questionnaire-based ALSFRS-R scores. The LME results for VM, PA, and the CM all show a [strongly] significant declining trend over time. The CM's signal to noise ratio with a threshold of 0.25 had the lowest value of -0.76 and on average a monthly decline of 2.84% in total physical functioning compared to data at baseline [51% over an 18-month period]. Similarly, the relationship between the CM and gross motor skill movements is moderate to strong positive, while it is weak with non-gross motor skill movements. The results are a positive step towards the direction of understanding the progression of ALS and show that the AI is a suitable metric to quantitatively assess the disease progression. Simultaneously, remote monitoring is beneficial for lowering the burden of patients, enhance therapeutic trial, maximize information collection, and lowers the trial costs [9,10,12,16].

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