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ORIGINAL ARTICLE

Post-stroke fatigue: how it relates to motor fatigability and other modifiable factors in people with chronic stroke

M. Rahamatali[1] · N. De Bont[1] · M. Valet[2,5] · V. Halkin[4] · P. Hanson[3] · T. Deltombe[3] · T. Lejeune[1,2] · C. Selves[1,2]

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Abstract

Post-stroke fatigue (PSF) is a common symptom associated with disability and decreased quality of life. Distinction can be made between perceived fatigue and fatigability. The first aim of this study was to evaluate the prevalence of perceived fatigue and fatigability amongst patients with chronic stroke and to explore how these two parameters relate. The second aim was to study the relationship between modifiable factors (sleep disorders, anxiety, depression and activities of daily living) and fatigue in this population. Sixty-two patients with chronic stroke (> 6 months) were included. Perceived fatigue was evaluated using the Fatigue Severity Scale (FSS). Motor fatigability was assessed with the percent change in meters walked from first to last minute of the 6-min Walk Test and an isometric muscular fatigability test. Subjects also completed self-report questionnaires assessing anxiety and depression (Hospital Anxiety and Depression Scale—HADS), sleep quality (Pittsburgh Sleep Quality Index—PSQI) and activity limitations (ACTIVLIM-stroke). Seventy-one percent of participants presented PSF. There was no correlation between the FSS and motor fatigability. FSS significantly correlated with HADS-Anxiety ($\rho = 0.53$, $P < 0.001$), HADS-depression ($\rho = 0.63$, $P < 0.001$), PSQI ($\rho = 0.51$, $P < 0.001$) and ACTIVLIM ($\rho = -0.30$, $P < 0.05$). A linear regression model showed that the HADS-Depression, the PSQI and the ACTIVLIM explained 46% of the variance of the FSS. A high proportion of chronic stroke patients presents PSF, with no relation between their fatigue and fatigability. Perceived fatigue is associated with potentially modifiable factors: anxious and depressive symptoms, poor sleep quality and activity limitations. Registered at ClinicalTrials.gov (NCT04277234) (21/02/2019).

Keywords Stroke · Fatigue · Fatigability · Depression

Introduction

Each year approximately 780,000 Europeans experience an initial or recurrent stroke [1]. In Belgium, 10,397 people suffer from stroke each year and 63,535 people live with stroke [1]. With improvements in the management of acute stroke in terms of rapidity of intervention and diagnostic techniques, the survival rate is rising and people with disability are living longer [1, 2]. Therefore, understanding the long-term comorbidities of stroke survivors is of crucial interest. Post-stroke fatigue (PSF) is one of the most common complaints in this population, with a prevalence varying between 33 and 77% [3]. However, PSF remains poorly understood, with a complex aetiology and unclear underlying mechanisms [4–6]. Various factors are put forward to explain PSF, the most recurrent being sleep and mood disturbances [6].

Distinction can be made between perceived fatigue, defined as a subjective sensation of lack of energy interfering with the activities of daily living (ADL), and motor

M. Rahamatali and N. De Bont performed the same amount of work.

✉ T. Lejeune
thierry.lejeune@uclouvain.be

1 Service de Médecine Physique et Réadaptation, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium

2 Secteur des Sciences de la Santé, Institut de Recherche Expérimentale et Clinique, NeuroMusculoSkeletalLab (NMSK), Université Catholique de Louvain, Avenue Mounier 53, 1200 Brussels, Belgium

3 Service de Médecine Physique et Réadaptation, CHU UCL Namur Site Godinne, Yvoir, Belgium

4 Service de Médecine Physique et Réadaptation, CHU Ambroise Paré, Mons, Belgium

5 Service de Médecine Physique et de Réadaptation, Groupe Santé CHC, Liège, Belgium

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fatigability, defined as the decline in an objective measure of physical performance over time [7]. In people with multiple sclerosis (MS), a moderate correlation between neuromuscular fatigability and MS-related fatigue has been found [8, 9]. Nonetheless, the studies are limited by heterogeneous samples and methods with a significant inter-individual variability [9]. In contrast, the relationship between perceived fatigue and motor fatigability has not been studied in people with stroke.

Post-stroke fatigue (PSF) is associated with poor neurological prognosis, low quality of life (QOL), poor participation in rehabilitation programs and increased mortality [5]. Therefore, assessing fatigue is of utmost importance for caregivers managing patients with chronic stroke.

The first aim of this study was to evaluate perceived fatigue and motor fatigability, and to explore their relationship in patients with chronic stroke. The second aim was to analyse the association between modifiable factors (sleep disorders, anxiety, depression and ADL limitations) and fatigue in this population. A better understanding of the way these factors interact could lead to a more effective management of PSF.

Methods

Participants and setting

A multicentre, cross-sectional study was performed. Participants were recruited from three Belgian hospitals from July 2018 to August 2019. Patients with chronic stroke (≥ 6 months since stroke), aged 18–85 years, with a Mini Mental State Examination (MMSE) ≥ 22 and the ability to walk with or without an assistive device, were included. Patients presenting cognitive impairment interfering with the evaluation, any other central nervous system disorder and any other medical condition that could cause fatigue (i.e. chronic inflammatory systemic or neoplastic diseases), were excluded. The study was approved by local ethics committees (B403201834794) and registered at ClinicalTrials.gov (NCT04277234). The study was conducted according to the declaration of Helsinki.

Study protocol and variables

Participants were assessed by trained investigators (NDB, MV and MR). Patient's demographic and clinical characteristics were collected. Age, gender, time since stroke and initial stroke severity, assessed with the National Institute of Health Stroke Scale (NIHSS) [10], were gathered from the participant's medical records. Motor impairment, assessed with the Rasch validated short form of the Fugl–Meyer motor scale (S-FM) [11]; cognitive impairment, assessed with the Montreal Cognitive Assessment (MoCA) [12]; and disability, assessed with the modified Rankin Scale (mRS) [13], were assessed. Subjects completed a battery of self-report questionnaires: the Fatigue Severity Scale (FSS) [14, 15] to assess fatigue, the Hospital Anxiety and Depression Scale (HADS) [16] to evaluate anxious and depressive traits, the ACTIVLIM-stroke questionnaire [17] to evaluate ADL activity limitations, and the Pittsburgh Sleep Quality Index (PSQI) [18, 19] to assess sleep quality. Participants also underwent the 6-min Walk Test (6MWT) [20] and an isometric protocol performed on a stationary knee extensor dynamometer (Cybex®, CSMI, Stoughton, MA, USA) to evaluate the Neuro Muscular Fatigability Index (NMFI) [21]. The full assessment lasted approximately 90 min. Sufficient rest periods were allowed between tests to avoid a fatigue induction bias.

The FSS is a 9-item self-report questionnaire validated to assess fatigue among stroke patients [15]. Each item consists of a statement that is scored on a 7-points Likert type scale, with higher scores indicating more severe fatigue. The sum of the scores obtained for each item is divided by nine to obtain the average score. An average score ≥ 4 is considered as pathological fatigue [15]. The HADS is a self-report questionnaire with anxiety and depression subscales, each consisting of seven questions. Participants score each item from 0 (no symptoms) to three points (maximum impairment), focusing on emotional state in the past seven days. Cut-off scores of ≥ 8 for both subscales were recommended in the original publication of the HADS [16]. However, studies about HADS in stroke patients suggested that lower cut-off scores would be more appropriate in this population [22, 23]. Therefore, a cut off of ≥ 7 was used in this study. The ACTIVLIM-stroke questionnaire is a self-report 20-item Rasch-validated questionnaire, including activities related to self-care, transfer, mobility, manual ability and balance. Participants evaluate the perceived difficulty of performing each activity if carried out without technical or human assistance. Each item has three possible answers ('impossible', 'difficult' and 'easy'). The total score ranges from 0 to 100%. Higher scores indicate better performance in ADL [17]. The PSQI is a self-report questionnaire evaluating quantitative and subjective aspects of sleep over a one-month period. The score of seven components are added to provide a global score from 0 to 21. A global score > 5 indicates poor sleep quality [18, 19].

The 6MWT is a functional walking test that has been used in stroke studies as a measure of walking capacity and walking endurance following stroke [24]. The American Thoracic Society (ATS) guidelines published in 2002 were used for this protocol, except that a 20 m walkway was used, due to space restrictions [26, 27]. The distance walked each minute and the total distance walked were measured. Performance fatigability was assessed by the percentage of change in distance walked during the first and sixth minute. The 6MWT percent change score has been previously used to assess motor fatigability in a wide range of pathologies [20]. Based on a previous study evaluating walking-related fatigability in MS patients, a 6MWT percent change cut-off of ≥ 10% was used to define fatigability [26].

The NMFI assesses motor fatigability by asking the participants to perform a maximal isometric contraction of the knee extensors on a dynamometer, according to the protocol proposed by Surakka et al. [21]. The administration was slightly modified from the original protocol, by asking a contraction of 45 s instead of 30 s, as the authors suggested that this would be more appropriate in the evaluation of people with disabilities. Only the non-affected limb was tested. The NMFI is calculated by the ratio between the putative torque-versus-time rectangular area if the subject had maintained the maximal torque recorded during the first 5 s for 45 s, and the actual area under the torque-versus-time curve (Fig. 1). This ratio is expressed as a percentage. A higher NMFI score indicates greater fatigability.

Statistical analysis

The data were analysed using SPSS for Windows version 23 (Chicago, IL, USA). The data normality was verified with the Kolmogorov–Smirnov test. Descriptive statistics were calculated for the total group. The strength of the relationship between FSS and performance fatigability, as well as between FSS and other factors, was examined using Pearson (parametric variables) and Spearman (non-parametric variables) correlation analysis. Variables that significantly associated with FSS were then considered as potential independent variables in a post hoc multiple linear regression analysis, with FSS as the dependent variable (high correlation: $0.7 < \rho < 0.9$, moderate correlation: $0.5 < \rho < 0.7$, low correlation: $0.3 < \rho < 0.5$, negligible correlation: $\rho < 0.3$) [28]. The difference between distances covered during each minute of the 6MWT was tested using repeated measures ANOVA and Holm–Sidak post hoc analysis.

Results

Sixty-two individuals completed the study protocol. Table 1 shows the demographic and clinical characteristics of the participants as well as the descriptive statistics of the experimental variables. Participants had a mean age of 59 ± 11 years. They presented with mild-to-moderate stroke (NIHSS 9 ± 6, MoCA 24 ± 3) and slight disability (mRS 2 ± 1).

Forty-four of the 62 participants (71%) had PSF (FSS ≥ 4). Subjects achieved an average distance of 386 ± 134 m on the 6MWT. Figure 2 illustrates the performance at each minute on the 6MWT. Repeated measures ANOVA and post hoc tests showed difference between the first and second minute ($P = 0.002$) and between the second and sixth minute ($P = 0.038$). Total distance walked during the last minute compared with the first minute decreased by 5.8 ± 11%. Fourteen of the 62 subjects (22.6%) presented fatigability on the 6MWT (6MWT percent change score ≥ 10%). The mean NMFI of the population was 25 ± 10%. Thirty-five of the 62 participants (56.4%) had anxiety (HADS-A ≥ 7) and 25 (40.3%) depression (HADS-D ≥ 7). Furthermore, 37 of the 62 participants (59.7%) had poor sleep quality (PSQI > 5).

FSS and motor fatigability

The results of the bivariate correlation analysis between FSS and fatigability measures are shown in Fig. 3. The 6MWT percent change score and the NMFI were not significantly associated with the FSS results ($P = 0.26$ and 0.20).

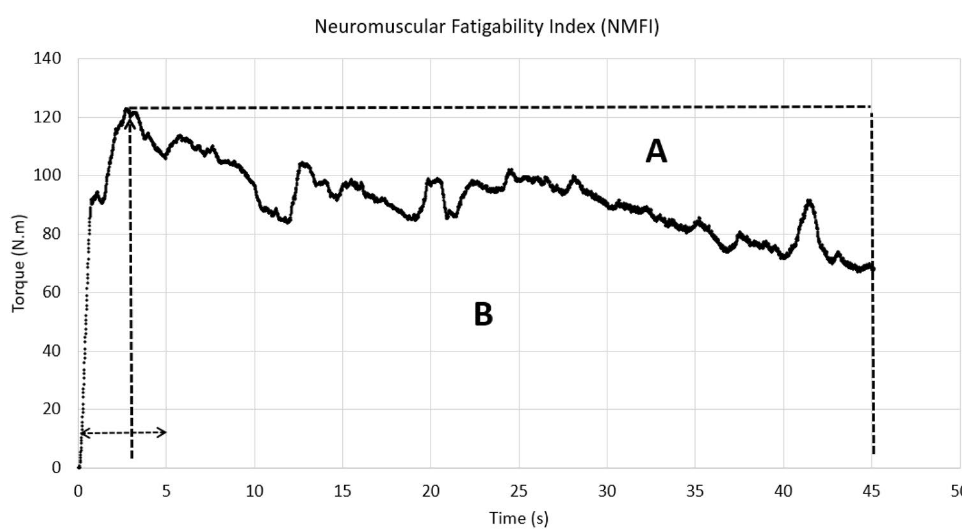

Fig. 1 Typical torque-versus-time curve. The NMFI is calculated by the ratio ($B/A + B$) between the putative torque-versus-time rectangular area if the subject had maintained the maximal torque recorded during the first 5 s for 45 s (A), and the actual area under the torque-versus-time curve (B)

Table 1 Characteristics of the participants ($n = 62$) and descriptive statistics of the experimental variables

Variables	Score
Age [mean (SD)] (years)	59 (11)
Women/men [*n* (%)]	25/37 (40/60)
Time since stroke [mean (SD)] (years)	4 (3.5)
Initial NIHSS [mean (SD)] (/42)	9 (6)
FM UL [mean (SD)] (%)	81 (26)
FM LL [mean (SD)] (%)	86 (21)
MoCA [mean (SD)] (/30)	24 (3)
mRS [mean (SD)] (/6)	2 (1)
FSS [mean (SD)] (/7)	4.5 (1.5)
Fatigued (FSS ≥ 4) [*n* (%)]	44 (71)
HADS-D [mean (SD)] (/21)	6 (4)
HADS-A [mean (SD)] (/21)	7 (4)
PSQI [mean (SD)] (/21)	7 (4)
Depressive symptoms (HADS-D ≥ 7) [*n* (%)]	25 (40.3)
Anxious symptoms (HADS-A ≥ 7) [*n* (%)]	35 (56.4)
Poor sleep quality (PSQI > 5) [*n* (%)]	37 (59.7)
ACTIVLIM [mean (SD)] (%)	70 (13)
6MWT [mean (SD)] (meters)	386 (134)
6MWT 1′–6′ % change [mean (SD)]	5.8 (11)
6MWT 1′–6′ % change ≥ 10% [n (%)]	14 (22.6)
NMFI [mean (SD)] (%)	25 (10)

SD standard deviation, *NIHSS* National Institutes of Health Stroke Scale, *FM* Fugl–Meyer (*UL* upper limb, *LL* lower limb), *MoCA* Montreal Cognitive Assessment, *mRS* modified Rankin Scale, *FSS* Fatigue Severity Scale, *HADS* Hospital Anxiety and Depression Scale (*D* depression, *A* anxiety), *PSQI* Pittsburgh Sleep Quality Index, *6MWT* 6-min walk test, *NMFI* Neuromuscular Fatigability Index

FSS and other parameters

FSS presented a moderate correlation with HADS-A ($\rho = 0.53$, $P < 0.001$), HADS-D ($\rho = 0.63$, $P < 0.001$), PSQI ($\rho = 0.51$, $P < 0.001$) and a low inverse correlation with ACTIVLIM ($\rho = -0.30$, $P < 0.05$) (Fig. 3). In the multiple linear regression model, HADS-D, PSQI and ACTIVLIM were significant correlates of FSS, accounting for 46% of the variance ($P < 0.001$) (Table 2 and Fig. 4).

Discussion

The first aim of this study was to evaluate perceived fatigue and motor fatigability and to explore how these two parameters relate amongst patients with chronic stroke. Seventy-one percent of the patients suffered from PSF, as evaluated by the FSS. Twenty-three percent presented walking-related fatigability, as assessed by the percent change in score between the first and last minute of the 6MWT. No correlation was found between perceived fatigue and motor fatigability in this population. The second aim was to explore the relationship between chosen modifiable parameters and fatigue in patients with chronic stroke. These results confirm previous findings that PSF correlates with activity limitations, sleep disturbances, depressive and anxious traits [3, 6].

The prevalence of perceived fatigue in this study's population (71%) is at the higher range of that found in the literature (33–77%) [3, 29, 30]. The use of different questionnaires to assess fatigue may explain a part of the variation between studies. There is a lack of homogeneity regarding the evaluation tools for PSF, with some of the most frequently used being the Fatigue Severity Scale (FSS), the Neurological Fatigue Index (NFI) and the Fatigue Impact Scale (FIS) [5,

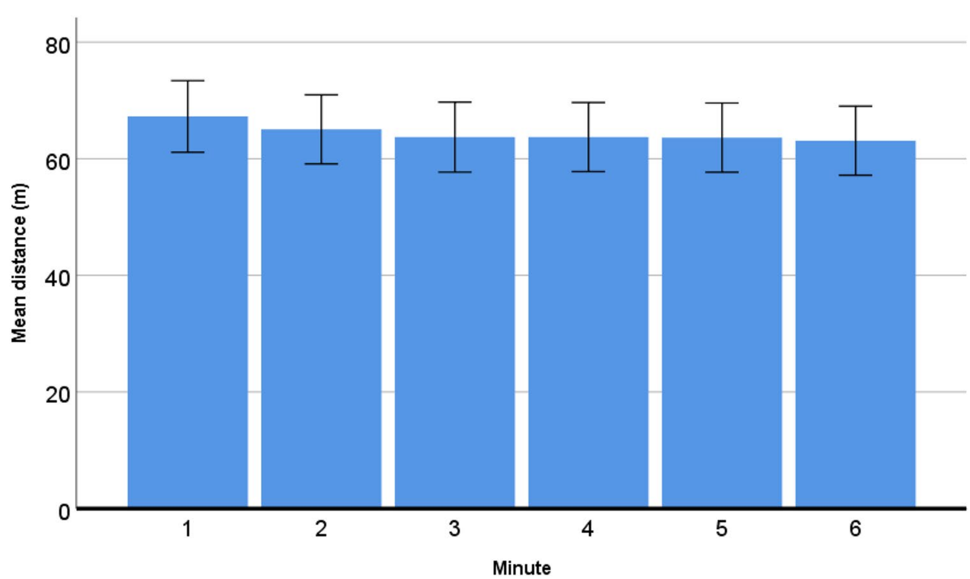

Fig. 2 Distance walked every minute (mean ± 1 standard deviation) during the 6-min walk test (6MWT)

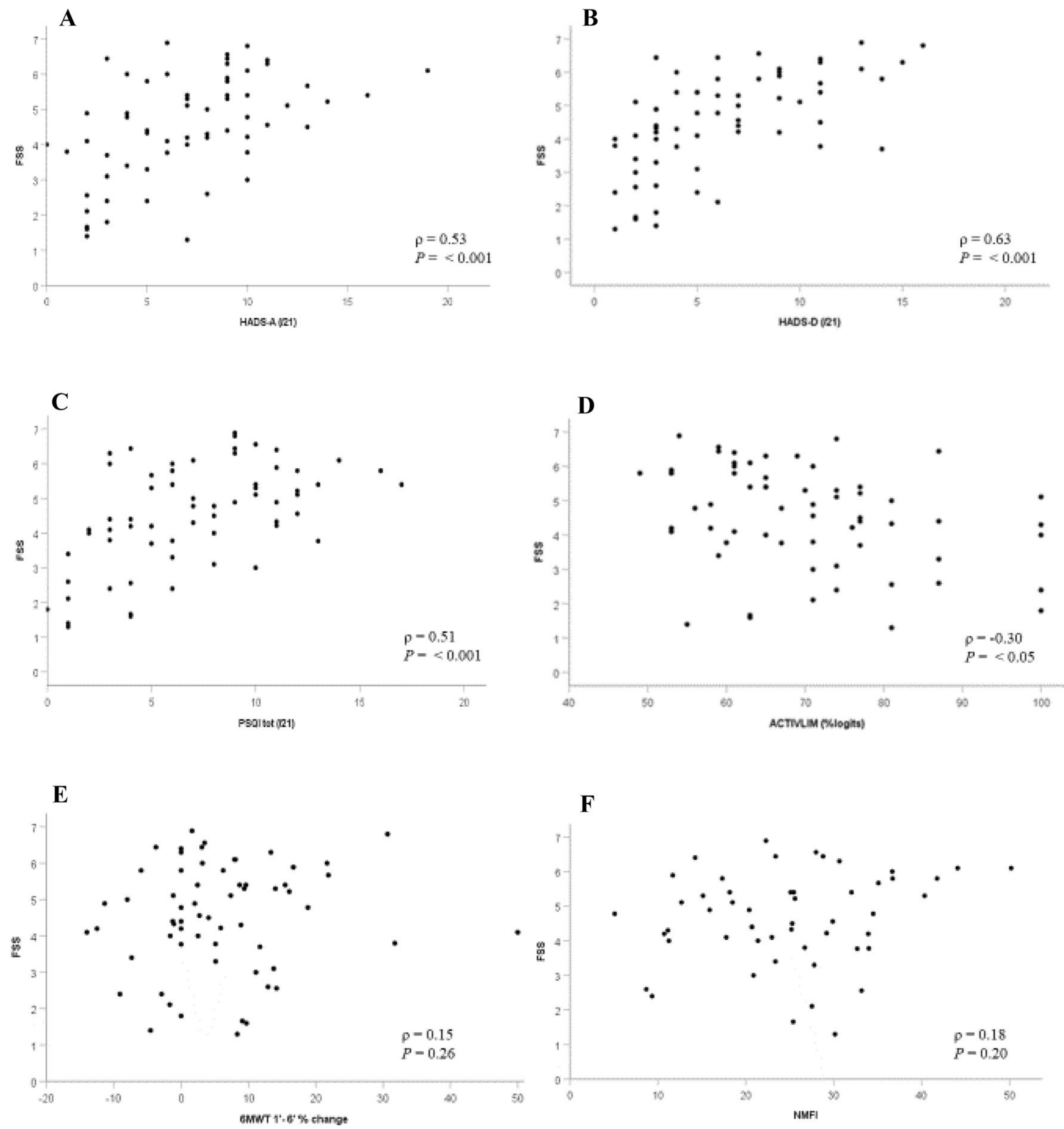

Fig. 3 **a** Correlation between FSS and HADS-A. **b** Correlation between FSS and HADS-D. **c** Correlation between FSS and PSQI. **d** Correlation between FSS and ACTIVLIM. **e** Correlation between FSS and 6MWT 1′–6′ % change score. **f** Correlation between FSS and NMFI. Correlation coefficient and significance level is shown for each figure

Table 2 Multiple linear regression analysis with FSS as the dependent variable

Independent variables	Dependent variables FSS		
	B	*β*	*P*
HADS-D	0.158	0.42	< 0.001
ACTIVLIM	− 0.021	− 0.18	0.06
PSQI	0.121	0.33	0.002

HADS-D Hospital Anxiety and Depression Scale-Depression, *PSQI* Pittsburgh Sleep Quality Index

6]. However, the FSS has shown good psychometric properties in PSF and thus was chosen for this study [15]. Nonetheless, our results were higher than the 36% found by Chen et al. [3] who also used the FSS. In their study, the population's characteristics were quite similar to ours except for socio-cultural aspects, as they studied a Chinese population. A study by Karasz et al. showed that in New York City, fatigue perceptions differed between European Americans and South Asians Americans due to differences in cultural models of health and illness, despite them living in the same city [31]. This illustrates the importance of cultural influence

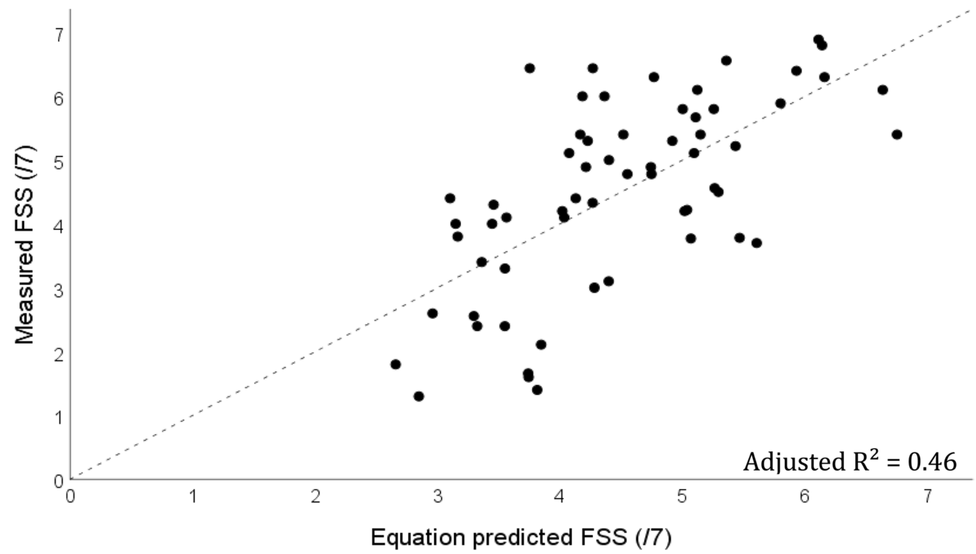

Fig. 4 Linear regression model with FSS as the dependent variables and HADS-D, PSQI and ACTIVLIM as independent variables

in the perception of fatigue, which could account for the difference between our results (71%) and the ones found by Chen et al. (36%). The high prevalence found in our study is an important finding, as fatigue seems to be present regardless of the severity of the motor or cognitive impairment. Although cognitive impairment has been found to correlate with PSF, in more severely impaired patients, one could argue that the validity of a self-report questionnaire might be lower, as the prevalence of anosognosia might be higher in these patients [32, 33]. These results comfort previous findings regarding the high incidence of PSF, even in mildly impaired patients, thus underlying the importance of screening for fatigue in this population [32, 33]. However, more data are needed in order to understand certain differences in prevalence found in the literature. Socio-cultural aspects have been less studied and should also be considered, as they may impact fatigue assessment.

To our knowledge, this is the first study to investigate the relationship between perceived fatigue and motor fatigability in patients with chronic stroke. Our findings indicate that there is no correlation between these factors. If evaluated by muscle strength, fatigability is inversely related to the initial strength developed (i.e. stronger individuals will present higher fatigability than their weaker pairs) [34–36]. Patients with MS or with cerebral palsy present lower fatigability than healthy subjects [36, 37]. Fatigability has a central and a peripheral component. The central component determines the ability of the central nervous system to adequately drive motoneurons during a task. The peripheral components take place at the muscle level and can be influenced by the type of muscle fibres and the contraction mode [38–40]. Isometric contractions have been shown to generate central fatigue, whereas concentric contractions tend to generate peripheral fatigue [39]. This implies that the physical performance measure chosen to evaluate fatigability might influence the component that is being measured. In this study, the 6MWT was used, which includes various modes of muscle contraction and is more relatable to daily life activities. Twenty-three percent of the participants to this study presented ≥ 10% change between the 1st and last minute on the 6 MWT.

The NMFI is another tool that can be used to assess fatigability. It assesses motor fatigability through a maximal isometric contraction of the knee extensors on a dynamometer. To our knowledge, there are no published norms for the NMFI computed on a 45″ period. However, our results on this fatigability index (25 ± 10%) are similar to that obtained in healthy subjects on a 30″ period (right knee 20 ± 7%, left knee 21 ± 12%) [21]. Comparatively, the mean NMFI of our stroke population was lower than the one observed in MS (31.3 ± 9.25%) [8]. This suggests that mild-to-moderate patients with chronic stroke may not be more fatigable than the healthy population when studying the motor aspect in the lower limb during 45″.

Fatigue is a subjective sensation of lack of energy that interferes with ADL, which underlying mechanisms are less known [7]. Both motor and cognitive deficits are associated with PSF [32]. It is a self-report subjective symptom not correlated to fatigability, a more objective measure of neuromotor deficit. This study's population presented with mild neurological impairments and fatigability was relatively low. It might be interesting to evaluate fatigability in more severely impaired patients to assess whether this parameter is related to the severity of the neurological impairment [6]. Fatigue, on the other hand, was highly prevalent in our population, despite mild neurological impairment. The choice of tools used to assess fatigability could also account for the low fatigability levels in this population. For instance, the 6MWT may not have been sufficient to induce fatigability in this population. The pacing pattern of the participants shows that meters walked during the first minute were higher than during any other minute of the test, then dropped during the second minute and remained stable until the end of the test. We did not observe a progressive decline in meters walked over time. This may be due to our study sample, where participants presented mainly mild neurological impairments and limitations. Indeed, Goldman et al. showed that, in patients with MS, a decline in speed was only observed in patients with moderate-to-severe neurological impairment (Expanded Disability Status Scale $\geq$ 4) [41]. They also observed that MS patients with mild neurological impairment and healthy subjects slowed down after the first minute, then accelerated in the final minute to their original speed or greater [41]. Further studies are needed to explore the pacing pattern on the 6MWT in stroke patients according to their neurological impairment. This lack of decline in speed on the 6MWT may also be explained by the study protocol based on the ATS guidelines, where the patient is told to walk the furthest distance but not as fast as possible [25]. In order to assess the motor fatigability, it might be more appropriate to modify these guidelines to emphasise on speed and to maximise effort, as proposed by Goldman et al. and Aldughmi et al. in studies evaluating fatigability in MS patients [41, 42]. In the future, it would be interesting to study simultaneously central fatigability, using isometric muscular contraction and peripheral fatigability, using concentric muscular contraction, on both sides.

Limitation in activities, assessed by the ACTIVLIM-stroke scale, was found to correlate with PSF. This is the first study, to our knowledge, to use this scale to evaluate the relationship between PSF and ADL. This scale presents good psychometric properties, as demonstrated by Batcho et al. [17], and has a better test–retest reliability compared to the Chinese version of Lawton ADL scale, used by Chen et al. [3]. However, one can argue about the sense of the relationship between fatigue and ADL limitations. Indeed, it remains unclear whether PSF makes patients less active or if limitations in activities enhance PSF, given the considerable increase in energy demands to perform ADL when presenting neuromotor impairments [43].

Regarding overall sleeping disorders, as assessed by the PSQI, 60% of our population had poor sleep quality which is also in the high range of the prevalence found in other studies (33–62%) [6]. A significant statistical correlation was found between FSS results and PSQI. This confirms that managing sleeping problems in patients with PSF is highly important. However, it remains difficult to explain whether PSF is a cause or a consequence of poor sleep quality.

Regarding mood disturbances, Wu et al. and van der Werf et al. showed that, despite there being a correlation between PSF and poststroke depression or anxiety, it does not make PSF a secondary disorder [44, 45]. De Doncker et al. gave the example that almost everyone with depression reports fatigue, but not all with fatigue have depression [6]. In a clinical context, this should be considered in order to screen and manage each disorder independently and more specifically.

Limits

There are some limitations to the present study. Firstly, due to the different evaluation tools used in our protocol, which needed sufficient motor and cognitive skills, a selection bias may have been induced. Indeed, the study sample is made of patients with mild to moderate disability. Therefore, the study findings may not be generalised to every chronic stroke patient. Secondly, there is a lack of valid measures to evaluate motor fatigability in stroke patients. In this study, we used tools previously validated to assess fatigability in populations with neurological impairments but not specifically in stroke patients. Thirdly, the absence of an a priori sample size calculation may represent another flaw to this study. However, a post hoc analysis showed that with a sample size of 62, a power of 80% was reached for a correlation $\geq$ 0.35 ($P = 0.05$). Lastly, the three assessors were trained to conduct the study protocol, however a pre-study inter-rater reliability evaluation was not performed.

Conclusion

PSF is highly prevalent in people with chronic stroke, despite mild-to-moderate disability. Perceived fatigue correlates to anxious and depressive symptoms, poor sleep quality and activity limitations. When managing stroke patients, evaluating fatigue, anxiety, depression, sleep quality and activity limitations may allow the conception of a more tailored program. In clinical practice, a better management of PSF should improve quality of life of people with stroke.

Funding Not applicable.

Availability of data and material The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Ethics approval This study was approved by the local ethics committee of the Cliniques Universitaires Saint-Luc-Université Catholique de Louvain ("StLuc" on clinicaltrials.gov).

Informed consent Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data.

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