Health-Related Quality of Life and Fatigue After Transient Ischemic Attack and Minor Stroke

José M. Ramírez-Moreno, MD, PhD,*,†,‡ Pedro Muñoz-Vega, MD,§ Sandra Bartolomé Alberca, PsyD,† and Diego Peral-Pacheco, MD, PhD||

Background: Studies suggest that fatigue and cognitive impairment may be present after transient ischemic attack (TIA) or minor stroke, but little is known about consequences in daily life. The main aim was to explore the presence of fatigue, cognitive impairment, and consequences in daily life after minor stroke-TIA. *Methods:* Patients (n = 92) were consecutively recruited from the Stroke Unit and were assessed within 2 weeks of hospital admission for first-ever and 3 months later. Control participants (n = 89) were recruited from the same population as the patients. Measures included the Fatigue Assessment Scale (FAS), Montreal Cognitive Assessment (MoCA), and The European Quality of Life index (EQ-5D-5L). *Results:* The prevalence of substantial fatigue was 65.2% (confidence interval [CI] 95%: 54.6%-74.8%) and extreme fatigue was 20.7% (CI 95%: 12.9%-30.4%) in minor stroke-TIA patients. The prevalence of substantial fatigue in controls was 23.5% (CI95%: 15.0%-34.0%) and extreme fatigue was 4.5% (CI 95%: 1.8%-11.0%). The mean (SD) score on the MoCA was 24.1 (3.2) for the patients group and 27.3 (2.4) for controls ($P < .001$). FAS showed the strongest negative correlation score with the EQ-5D-5L index ($r = -0.480$; $P < .0001$), higher levels of mental and physical fatigue are associated with lower EQ-5D-5L index ($r = -0.376$; $P < .001$ and $r = -0.497$; $P < .001$, respectively). The correlations between the FAS and the MoCA measures were no significant. MoCA was not significantly correlated with EQ-5D-5L. *Conclusions:* Fatigue was a very common symptom in TIA/minor stroke patients. The fatigue had a significant impact on the health-related quality of life construct in its entirety, even after accounting for the influence of several factors.

Key Words: Health-related quality of life—fatigue—cognitive impairment—TIA—minor stroke—stroke outcome measures

Introduction

Fatigue is very common poststroke phenomenon, with significant implications for quality of life.[1-3] The frequency of self-reported fatigue is roughly twice as high in patients poststroke as in matched control subjects.[4] Poststroke fatigue often poses a barrier to return to work and reduced physical function, daily activities, quality of life, and rehabilitation potential.[1,4-9]

Transient ischemic attack (TIA) and minor stroke is associated with an increased risk of subsequent stroke, and treatment is focused on secondary stroke prevention.[10] It is currently assumed that patients do not experience any TIA-induced sequela; however, patients have reported residual impairments after these minor events.[11] Although fatigue is important to patients, research has been limited,[9] partly perhaps because of difficulties in measurement and in unscramble the numerous potential causes.[12]

From the *Extremadura University Medical School, Department of Biomedical Sciences, Badajoz, Spain; †Hospital Universitario Infanta Cristina, Stroke Center, Neurology Department, Badajoz, Spain; ‡Multidisciplinary Research Group GRIMEX, Extremadura, Spain; §Hospital de Neurorehabilitación Casaverde, Mérida, Spain; and ||Extremadura University Medical School, Department of Medical-Surgery Therapeutics, Badajoz, Spain.

Received August 27, 2018; revision received September 18, 2018; accepted September 27, 2018.

Sources of Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: None.

Address correspondence to José M. Ramírez-Moreno, MD, PhD, Extremadura University Medical School, Department of Biomedical Sciences, Avda. de Elvas s/n., 06080 Badajoz, Spain. E-mailes: jramrez@unex.es, j.ramrez@gmail.com, pedromv20@hotmail.com, sandrabartolomealberca@gmail.com, diego@unex.es.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.046

A recently conducted systematic review have investigated the prevalence of fatigue and cognitive impairment following TIA and minor stroke suggesting these patients experience residual impairments. However, existing studies have important limitations because few studies included a control group and there is a paucity of studies determining predictors of poststroke fatigue.[13]

The fatigue probably results from complex, poorly understood interactions between biological and psychosocial event. We consider that it is important to try to understand fatigue more deeply and thus identify at-risk patients. Our aim was to explore the presence of fatigue, cognitive impairment, and consequences in daily life following clinically diagnosed TIA or minor stroke at 3 months after the event, and to identify predictors of fatigue.

Methods

Patients were consecutively recruited from the Stroke Unit at the Infanta Cristina University Hospital (Badajoz, Spain) between 1 January 2016 and 1 November 2017.

The population consisted of patients aged 18 years and over with a first-ever diagnosis of TIA or minor stroke. The patients were diagnosed according to the clinical practice guidelines, and the study population was restricted to patients with a minor ischemic stroke (National Institutes of Health Stroke Scale score ≤3 at admission). In accordance with these guidelines, all patients underwent neurological examination and brain imaging at the time of their index event. Radiological findings were used to differentiate between ischemic and hemorrhagic stroke. Patients were excluded if the physician's examination revealed aphasia, or any circumstance that would make evaluation unreliable, or if they were not going to be followed up at our outpatient clinic. Control participants were recruited from the same population as the patients, among the patients' spouses, relatives, or social environment. This is a nonmatched case-control study in which we enroll controls without regard to the number or characteristics of the cases. Controls had to be at least 18 years old, without a history of TIA or stroke and they were all living independently.

All patients were invited to visit our research center for a follow-up examination at 3 months after the event. Data were collected by means of a standardized, structured questionnaire.

Assessment Instruments

The Fatigue Assessment Scale (FAS) was used to assess experience of fatigue. The FAS is a 10-item general fatigue questionnaire to assess fatigue. Five questions reflect physical fatigue and 5 questions (questions 3 and 6-9) assess mental fatigue. The total score ranges from 10 to 50. A total FAS score less than 22 indicate no fatigue, and a score greater than or equal to22 indicates fatigue (2 subgroups, fatigue: scores 22-34 and extreme fatigue: scores ≥35). The use of the FAS to measure fatigue after stroke is recommended because it is feasible for most of patients, and it has a good test-retest reliability and high construct validity.[14]

The Montreal Cognitive Assessment (MoCA) was used to determine cognitive impairment in 8 cognitive domains. This screening instrument is composed of 30 items with score range from 0 to 30. Scores of 25 or below indicate impairment. MoCA is broadly used and has good sensitivity and specificity. The MoCA is easy and quick to use and detects a higher rate of patients as cognitively impaired compared with the MiniMental State Examination (MMSE) in the acute poststroke setting.[15]

The European Quality of Life-5 Dimensions-5 Levels index score (EQ-5D-5L) is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments.[16] The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale. This can be used as a quantitative measure of health outcome that reflects the patient's own judgment. The scores on these 5 dimensions can be converted to a single summary index number. The EQ-5D-5L descriptive system is a valid health outcome measure in patients experiencing acute stroke, with some psychometric advantages in comparison with others scales.[17]

Other Measurements

Educational level was classified into 3 categories. These groups approximately corresponded to levels 0-2 (preprimary, primary, and lower secondary education), 3 (upper secondary education), and 4-6 (postsecondary education). We defined physical activity levels into sedentary activity, light activity, moderate, and vigorous activity. To determine the socio-familial risk, the modified Gijón scale was applied.[18] Functional outcome was assessed with the modified Rankin Scale. Hypertension was defined as a history of high blood pressure (≥140 of 90 mmHg) reported by the participant or the current use of antihypertensives. Dyslipidemia was defined as the current use of statins, total cholesterol greater or equal to 5.7 mmol/L, serum triglyceride greater or equal to 1.7 mmol/L, or low-density lipoprotein greater or equal to 3.1 mmol/L. Diabetes mellitus was defined by previous diagnosis, treatment with insulin/oral hypoglycemic medications, or a fasting plasma glucose level greater or equal to 126 mg/dL or glycosylated hemoglobin greater or equal to 6.5%. Atrial fibrillation was reported by the participant or indicated by electrocardiogram. We defined smoking by either the current or former practice of smoking, and regular alcohol consumption defined as greater or equal to 3 times/week was assessed. Body mass index was defined

by weight/(length^2). Depression was considered if reported by the participant or by current use of antidepressant medication. Self-reported family history of stroke. Self-reported family history of dementia.

The study was approved by the Research Ethics Committee. Written informed consent was obtained from all participants prior to their inclusion.

Analysis

Descriptive analysis was used for continuous variables (*t* tests) and X test for categorical variables. Logistic regression analysis was used to determine predictors of fatigue at 3 months poststroke. Predictive models were developed by first running univariate analyses between the outcome (presence or absence of fatigue) and each potential predictor. If the probability value was lower of .2, the predictor was then considered for inclusion in the multivariate model. Correlations between each of the predictors were then checked and only the predictor with the most significant contribution to the model was included if there was a high correlation between the predictors. The remaining predictors were then entered in a stepwise manner until no variable excluded from the model made a significant contribution. Age and sex were forced into the model, because these were identified as important confounding variables and general practice was included as a random effect.

To determine variables potentially predictive EQ-5D-5L, multiple linear regressions (forward-stepwise selection) were performed. The variables relevant to the models were selected from the univariate analysis, based on a threshold *P* value less or equal to .20. The final models incorporated the standardized beta coefficients. The independent variables with the higher standardized beta coefficients are those with a greater relative effect on health-related quality of life (HRQL).

The statistical analyses were performed using the SPSS software package version 22.0 (SPSS Inc., Chicago, IL). All tests were 2-sided. Statistical significance was defined as *P* less than.05.

Results

Study Population

Of 200 eligible participants who were approached, 181 consented to the study. Ninety-two patients had minor stroke (n = 60) or TIA (n = 32), and 89 was controls. Baseline characteristics are shown in Table 1. There were significant differences in demographic characteristics (sex and education level), physical activity intensity, vascular risk factors (hypertension, diabetes, coronary heart disease, and smoking), and social circumstances. There were no significant differences in age, area of residence, body mass index, hyperlipidemia, atrial fibrillation, coronary heart disease, alcohol consumption, depression, family history of stroke, and family history of dementia.

Fatigue, Cognitive Impairment and Health-Related Quality of Life

Fatigue scores at the 3-month follow-up were significantly higher in patients with minor stroke or TIA than in controls (odds ratio, 1.49; 95% confidence interval [CI], 1.34-1.68; $P < .0001$). The prevalence of substantial fatigue was 65.2% (CI95%: 54.6%-74.8%) and extreme fatigue was 20.7% (CI95%: 12.9%-30.4%) in patients with minor stroke or TIA. The prevalence of substantial fatigue in controls subjects was 23.5% (CI95%: 15.0%-34.0%) and extreme fatigue was 4.5% (CI95%: 1.8%-11.0%). The mean (SD) score on the MoCA was 24.1 (3.2) for the minor stroke-TIA group and 27.3 (2.4) for the control group ($P < .001$). The cases scored on average lowest in delayed recall, visuospatial/executive, language, and abstraction subcategories of the MoCA. Mean (SD) EQ-5D-5L index for patients with minor stroke-TIA was .85 (.15) and .97 (.1) for controls. The differences were statistically significant ($P < .001$) and of great magnitude between the groups. Also, the differences in EQ VAS records were statistically significant between the groups ($P < .001$; Table 2).

Risk Factors Associated With Fatigue

Multivariate analysis using all clinical variables produced a model containing 5 variables that independently predicted fatigue at 3 months after the event: sex, social risk, dyslipidemia, smoking, and physical inactivity. The Hosmer-Lemeshow $\chi 2$ was 4.7 ($P = .697$) and the area under the curve was .74 (95% CIs, .66-.81; Table 3).

Association Between Fatigue and Quality of Life

In the patients, FAS showed the strongest negative correlation score with the EQ-5D-5L index (r = −.480; $P < 0.0001$), higher levels of mental and physical fatigue are associated with lower EQ-5D-5L index (r = −.376; $P < .001$ and r = −.497; $P < .001$, respectively). The correlations between the FAS score and the MoCA measures were no significant (r = −.026; $P = .806$). MoCA score was not significantly correlated with either EQ-5D-5L index or EQ VAS records (Table 4 and Fig 1).

The linear regression analysis for EQ-5D-5L showed that higher FAS index was associated with a decrease in EQ-index score, Beta −.012 (95% CI −.017 to −.007, $P = .0001$) and EQ-VAS score Beta −1.530 (95% CI −2.07 to −.979, $P = .0001$). Only the physical component of FAS index had a significant association with decline in EQ-index score and EQ-VAS score Beta −.022 (95% CI −.033 to −.018, $P = .001$) and Beta −2.460 (95% CI −3.770 to −1.160, $P = .0001$); respectively. The amount of variability in the HRQL score explained by variation in the models is small (adjusted R2 for the 4 models are: .23, .25, .24, .26

Table 1. *Clinical characteristics between cases and controls*

	Controls (n = 89)	Cases (n = 92)	*P*
• Age, y, mean (SD)	58.3 (7.7)	59.5 (8.2)	.317
• Male sex, n (%)	37 (43.0%)	66 (72.5%)	<.001
• Body Mass Index, mean (SD)	27 (4.1)	28 (3.9)	.166
• Rural residence, (%)	55 (61.8%)	44 (47.8%)	.073
• Social risk, (%)	19 (21.3%)	32 (34.8%)	.049
Education			
• Primary school and below (%)	20 (22.5%)	38 (41.3%)	.005
• Middle and high school (%)	58 (65.2%)	51 (55.4%)	
• Bachelor and above (%)	11 (12.4%)	3 (3.3%)	
Physical activity previous stroke			
• Sedentary (%)	14 (15.7%)	24 (26.1%)	<.0001
• Light intensity (%)	44 (49.4%)	62 (67.4%)	
• Moderate intensity (%)	31 (34.8%)	6 (6.5%)	
Medical history			
• Hypertension (%)	30 (33.7%)	54 (58.7%)	.001
• Hyperlipidaemia (%)	28 (31.5%)	40 (43.5%)	.125
• Diabetes (%)	14 (15.7%)	28 (30.4%)	.022
• Atrial fibrillation (%)	8 (9.0%)	11 (12.0%)	.630
• Coronary heart disease (%)	1 (1.1%)	12 (13.0%)	.002
• Smoking (%)	33 (37.1%)	59 (64.8%)	<.0001
• Alcohol consumption (%)	37 (41.6%)	52 (57.1%)	.039
• Depression (%)	11 (12.4%)	5 (5.4%)	.121
• Family history of stroke (%)	27 (30.3%)	25 (27.2%)	.743
• Family history of dementia (%)	24 (27.0%)	26 (28.6)	.869

Table 2. *Clinical variables in transient ischaemic attack/minor stroke and controls*

	Controls (n = 89)	Cases (n = 92)	*P*
Functional outcome			
mRS, median (IQR)	0 (0-0)	0 (0-1)	.110
Fatigue			
FAS, mean (SD)	18.5 (4.2)	30.4 (5.6)	<.0001
FAS physical, mean (SD)	9.9 (2.6)	16.1 (2.8)	<.0001
FAS mental, mean (SD)	8.7 (2.7)	14.4 (3.4)	<.0001
None (%)	65 (76.5%)	13 (14.1%)	<.0001
Substantial fatigue (%)	20 (23.5%)	60 (65.2%)	
Extreme fatigue (%)	4 (4.5%)	19 (20.7%)	
Cognition			
MoCA score, mean (SD)	27.2 (2.4)	24.1 (3.2)	<.001
Visuospatial/executive, mean (SD)	4.60 (0.6)	3.72 (1.1)	<.001
Animal naming, mean (SD)	2.97 (.2)	2.90 (.3)	.084
Attention, mean (SD)	5.54 (.8)	4.93 (1.2)	<.001
Language, mean (SD)	2.72 (.5)	2.35 (.7)	<.001
Abstraction, mean (SD)	1.52 (.6)	1.23 (.8)	.008
Delayed recall, mean (SD)	3.54 (1.4)	2.82 (1.8)	.004
Orientation, mean (SD)	5.93 (.3)	5.79 (.6)	.057
Quality of life			
EQ-5D-5L index, mean (SD)	.97 (.08)	.84 (.15)	<.001
EQ VAS records, median (IQR)	80 (20)	50 (20)	<.001

Abbreviations: EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels index score; EQ VAS, self-rated health on a vertical visual analogue scale; FAS, Fatigue Assessment Scale; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; SD, standard deviation; mRS, modified Rankin Scale.

Table 3. *Multiple variable regression model for predicting fatigue at 3 months*

	β (SE)	OR	95% CI		*P* (Lr)
Sex female	.594 (.347)	1.812	.917	3.579	.087
Physical inactivity	−.409 (.261)	2.408	1.178	4.920	.117
Social risk	.775 (.383)	2.171	1.024	4.603	.039
Hyperlipidaemia	.793 (.353)	2.210	1.107	4.412	.023
Smoking	.726 (.343)	2.067	1.056	4.048	.034

Potential predictors included: age, sex, education level, social risk, hypertension, dyslipidemia, smoking, physical activity, depression and body mass index. Hosmer-Lemeshow $\chi 2$: 4.7 (P = .697). Area under the curve: .74 (95% confidence intervals, .66-.81).

Abbreviations: β, regression coefficient; CI, confidence interval; Lr, likelihood ratio; OR, odds ratio; SE, standard error.

respectively). However, these models explain much more of the variance than those models in the controls subjects (adjusted R2 for the 4 models are: .056, .110, .057, .110 respectively). The lineal regression analysis for all 4 models is shown in Table 5 (only cases).

Discussion

We found that clinically diagnosed TIA/minor stroke patients were more likely than controls to fatigue, and cognitive impairment. Our findings suggest that, for many patients, TIA/minor stroke is not a transient event and patients experience impairments after initial symptoms have resolved. Further, fatigue was associated significantly with a poor HRQL.

The fatigue is a disease state characterized by a chronic, persistent, and excessive lack of energy[9,19] with an impact on activities of daily living.[20] Poststroke fatigue is generally defined in subjective terms as an overall state of feeling: "a feeling of early exhaustion, weariness, and aversion to effort."[21] Guidelines relevant to TIA promote rapid evaluation of patients with suspected TIA and focus on diagnosis, determining the affected vascular territory and assessing stroke risk.[22] Follow-up for TIA patients is focused on management of stroke risk factors.[23] However, our study suggests a relatively high prevalence of cognitive impairment and fatigue post-TIA/minor stroke.[11] Very few studies done so far had control group,[13] but, our work can determine that the prevalence of these alterations is higher than in people of a similar age without TIA/minor stroke.

Strengths of our study include the adequate sample size, with inclusion of both minor stroke and patients with TIA and the comparison with a stroke-free control group. Furthermore, the single center design allowed us to collect information systematically, limiting information bias and very low lost to follow-up. Being a tertiary referral center, our cohort is a representative sample of a stroke population.

However, some limitations need to be addressed. Bias may be introduced in our study because: (1) in this study design, the number of controls does not equal the number of cases, and controls were unmatched to cases on the basis of age, sex, or education. But, we took it into account to perform properly analytical methods for nonmatched case-control studies; (2) patients may be more conscious of their health following a TIA compared with controls, resulting in increased reporting of impairments; and (3) stroke prevention medication was not included as a confounder in the analysis. There is some evidence that beta-blockers, statins, sedatives drugs, and antidepressants may cause fatigue[24,25]; and (4) fatigue is also associated, either directly or indirectly, with anxiety, emotional, and behavioral symptoms; and these information was not included in the analysis. For many years, fatigue was considered to be a symptom of depression because the 2 conditions were often concomitant; patients with depression are slower and more tired than nondepressed patients.[21] Indeed, patients often confuse fatigue and depression.[25] Depression and fatigue might be 2 separate processes, and the temporal relationship between the 2 is not well understood.[26]

Table 4. *Pearson correlations among fatigue, cognitive status and health-related quality of life*

Cases (n = 92)	FAS	FASph	FASm	MoCA	EQ-5D-5L	EQ VAS
FAS	1					
FASph	.870**	1				
FAS m	.912**	.598**	1			
MoCA	−.026	−.120	.057	1		
EQ-5D-5L	−.480**	−.497**	−.376**	.092	1	
EQ VAS	−.488**	−.491**	−.394**	−.015	.364**	1

Abbreviations: EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels index score; EQ VAS, self-rated health on a vertical visual analogue scale; FAS, Fatigue Assessment Scale; FASph, FAS physical; FASm, FAS mental; MoCA, Montreal Cognitive Assessment.

**Significant difference level $P < .01$ (2-sided).

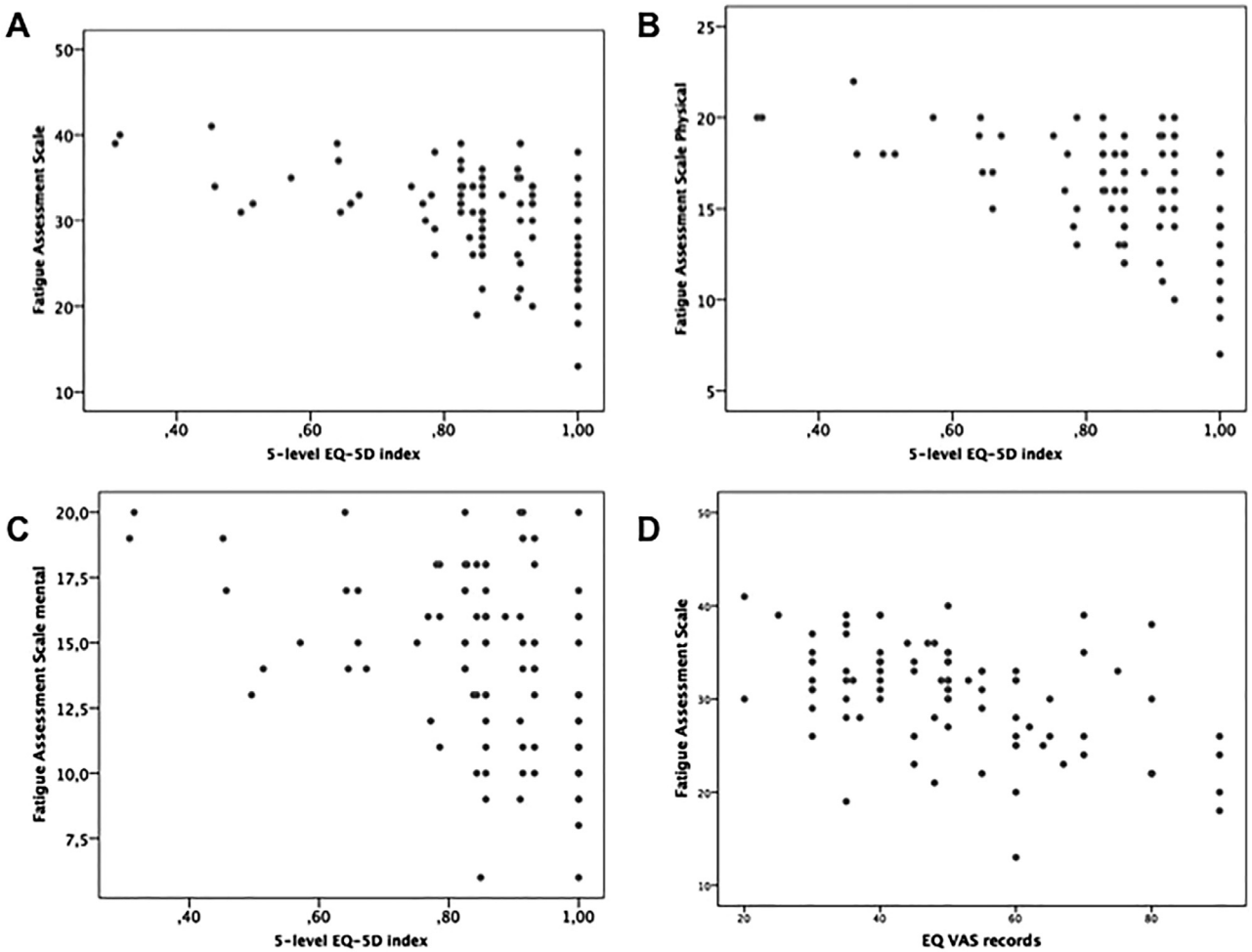

Figure 1. *A. Relationship between EQ-5D-5L (Higher scores indicate better health status) and FAS score (Higher scores indicate much more fatigue). (Pearson correlation coefficient −.480,* P = *.0001). B. Relationship between EQ-5D-5L (higher scores indicate better health status) and FAS physical score (Higher scores indicate much more physical fatigue). (Pearson correlation coefficient −.497,* P = *.0001). C. Relationship between EQ-5D-5L (higher scores indicate better health status) and FAS mental score (higher scores indicate much more mental fatigue). (Pearson correlation coefficient −.376,* P = *.0001). D. Relationship between EQ-VAS (higher scores indicate better self-rated health on a vertical visual analogue scale) and FAS score (higher scores indicate much more fatigue). (Pearson correlation coefficient −.488,* P = *.0001). EQ-5D-5L, European Quality of Life-5 Dimensions − 5 Levels index score; FAS, Fatigue Assessment Scale.*

Table 5. *Linear regression analysis for the association betweeen fatigue and quality of life at 3-month follow-up*

(Cases, n = 91)	EQ-5D-5L*			EQ VAS**		
Variables	Beta	(95% CI)	*P* value	Beta	(95% CI)	*P* value
MODEL 1†						
FAS	−.012	−.017 to −.007	.0001	−1530	−2.07 to −.979	.0001
Sex	.040	−.022 to .105	.196	-	-	-
Social risk	−.027	−.086 to .032	.370	6070	−.370 to 12.5	.065
MODEL 2††						
FASm	−.005	−.015 to .005	.355	-.767	−1.870 to .320	.165
FASph	−.022	−.033 to −.01	.001	−2.460	−3.77 to −1.160	.0001
Sex	.045	−.018 to .108	.156	-	-	-
Social risk	−.025	−.084 to .034	.402	6.210	−.190 to 12.60	.057

The analyses were adjusted for age, sex, education level, social risk, and MoCA test.

Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels index score; EQ VAS, self-rated health on a vertical visual analogue scale; FAS, Fatigue Assessment Scale; FASph, FAS physical; FASm, FAS mental; F, global significance test; MoCA, Montreal Cognitive Assessment; R^{2adj}, adjusted coefficient of determination.

*†ANOVA, F = 26.4; *P* = .001; R^{2adj} = .228.

**†ANOVA, F = 16.2; *P* = .0001; R^{2adj} = .252.

*††ANOVA, F = 28.9; *P* = .0001; R^{2adj} = .239.

**††ANOVA, F = 16.6; *P* = .0001; R^{2adj} = .257.

Sex female, physical inactivity, social circumstances, hyperlipidemia, and smoking were independently associated with fatigue in a logistic regression model. Importantly, the factors we identified accounted for an important predictive ability in fatigue (area under the curve: .74). Several studies showed that fatigue is more common in women,[27,28] while others not find any differences in gender among stroke whit and without fatigue.[4,9,12] In theory, low level of physical activity may cause fatigue.[26] The association between fatigue after stroke and physical fitness is uncertain. One study found an association between fatigue and reduced lower limb extensor power.[29] Another study found that stroke survivors with higher levels of fatigue were more likely to have lower self-efficacy expectations for exercise and, therefore, were less likely to participate in physical activity.[30] A review of cross-sectional studies found neither current physical activity levels nor cardiorespiratory fitness explained the level of fatigue experienced by people after stroke.[31] The impact of social factors on fatigue has also been addressed in a few studies but the results remain to be confirmed. Studies failed to demonstrate a link between fatigue and marital status,[32,33] and only 1 paper work found this type of association.[34] The authors of the latter study further postulated that fatigue might be more frequent in patients living alone.[34] Lack of social support was associated with more fatigue.[9] Another study showed a higher incidence of fatigue in patients with dysfunctional familial relationships, patients with a lower family income, and patients living in rural areas.[35] Although vascular risk factors might conceivably be involved in poststroke fatigue, the results tend to argue against this hypothesis.[25] An association with hyperlipidemia was found in 1 study[36] but not in others[9] and smoking was associated with fatigue in 1 study[9] but not in others.[35,37]

According to previous studies where fatigue was found equally common in patients with TIA as in patients with ischemic stroke,[38] or was more frequent in patients with TIA,[3] it appears that stroke characteristics (such as the type, severity, etiology, and infarct volume) are not predictive of fatigue.[25]

Our findings suggest that prestroke health is an important factor in development of fatigue. TIA/minor stroke patients were more likely to report fatigue than controls who had not experienced stroke. Our results also showed that stroke patients had more likelihood of having 2 or more other diseases. This finding suggests that the higher prevalence of fatigue may be at least in part related to the stroke population being in poorer health even before they had a stroke. The association between prestroke comorbidities and fatigue is not clear, as is referred in previous literature.[1,9,39]

There is little evidence that poststroke fatigue is directly associated with cognition; however, a recent synthesis of evidence suggested that fatigue may heighten the influence of depressive symptoms,[25] and therefore, there may be an indirect relationship between fatigue and cognition that is mediated by depressive symptoms.[40] Nevertheless, we found no correlation between the FAS score and the MoCA test, or between the mental and physical subscales FAS and the MoCA test, and neither in the individual assessment of the cognitive domains of the MOCA and FAS score.[41] Other studies also failed to observe correlations between fatigue questionnaire scores and the MMSE.[33,36,40] However, we know that the MMSE is not really sensitive to poststroke attention and executive disturbances.[15] The MoCA might provide a more sensitive

evaluation of the potential relationships between cognition and fatigue,[42] but this is not the case in our work.

Because TIA/minor stroke symptoms leave little or no permanent damage to the brain, TIA would be expected to have little impact on HRQL. However, we found that patients with TIA/minor stroke at 3 months have a significantly worse quality of life and worse self-perceived health compared to controls. In addition, our results showed that higher levels of fatigue were significantly associated with lower EQ-5D-5L and EQ VAS. In the multiple linear regression models fatigue was shown as the main predictor of HRQL, fundamentally the physical component. A report from Norway showed a near complete influence of fatigue on HRQL with only the HRQL domain on emotional role functioning exempt from the influence.[43] This apparent sweeping influence of fatigue on all the dimensions of HRQL was reported in others previous studies of stroke survivors.[44,45] These observations may be indicative of a really deep impact of fatigue on practically all aspects of HRQOL poststroke, which implies that addressing fatigue may go a long way in enhancing stroke patients' HRQL.

Conclusions

In conclusion, fatigue was a very common symptom in TIA/minor stroke patients. The outcome of this study showed that in spite of the multidimensional nature of health-related quality of life, fatigue had a significant impact on the HRQL construct in its entirety, even after accounting for the influence of several socio-demographic, clinical, and cognitive factors on HRQL. Therefore, reducing fatigue can be an important tool in order to enhance TIA/minor stroke patients' HRQL.

References

1. Appelros P. Prevalence and predictors of pain and fatigue after stroke: a population-based study. Int J Rehabil Res 2006;29:329-333.
2. Colle F, Bonan I, Gellez Leman MC, et al.. Fatigue after stroke. Ann Readapt Med Phys 2004;49:272-276.
3. Winward C, Sackley C, Metha Z, et al. A population-based study of the prevalence of fatigue after transient ischemic attack and minor stroke. Stroke 2009;40:757-761.
4. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. Arch Phys Med Rehabil 1999;80:173-178.
5. Van Zandvoort MJ, Kappelle LJ, Algra A, et al. Decreased capacity for mental effort after single supratentorial lacunar infarct may affect performance in everyday life. J Neurol Neurosurg Psychiatry 1998;65:697-702.
6. Van der Werf SP, van den Broek HL, Anten HW, et al. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. Eur Neurol 2001;45:28-33.
7. Ferrel B, Grant M, Dean G, et al. Bone tired. The experience of fatigue and its impact on quality of life. Oncol Nurs Forum 1996;23:1539-1547.
8. Michael KM, Allen JK, Macko RF. Fatigue after stroke: relationship to mobility, fitness, ambulatory activity, social support, and falls efficacy. Rehabil Nurs 2006;31:210-217.
9. Choi-Kwon S, Han SW, Kwon SU, et al. Post-stroke fatigue: characteristics and related factors. Cerebrovasc Dis 2005;19:84-90.
10. National Institute for Health and Clinical Excellence. Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) 2008.
11. Turner GM, Calvert M, Feltham MG, et al. Ongoing impairments following transient ischaemic attack: retrospective cohort study. Eur J Neurol 2016;23:1642-1650.
12. Carlsson GE, Moller A, Blomstrand C. A qualitative study of the consequences of 'hidden dysfunctions' one year after a mild stroke in persons <75 years. Disabil Rehabil 2004;26:1373-1380.
13. Moran GM, Calvert M, Feltham MG, al.. A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper. BMJ Open 2015;5:e008149.
14. Mead G, Lynch L, Greig C, al.. Evaluation of fatigue scales in stroke patients. Stroke 2007;38:2090-2095.
15. Pendlebury St, Cuthbertson Fc, Welch SJ, al.. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. Stroke 2010;41:1290-1293.
16. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-1736.
17. Golicki D, Niewada N, Buczek J, et al. Validity of EQ-5D-5L in stroke. Qual Life Res 2015;24:845-850.
18. García Gonzales JV, Diaz Palacios E, Salamea García A, et al. Evaluación de la fiabilidad y validez de una escala de valoración social en el anciano. Aten Primaria 1999;23:434-440.
19. Falconer M, Walsh S, Harbison JA. Estimated prevalence of fatigue following stroke and transient ischemic attack is dependent on terminology used and patient gender. J Stroke Cerebrovasc Dis 2010;19:431-434.
20. Lynch J, Mead G, Greig C, et al. Fatigue after stroke: the development and evaluation of a case definition. J Psychosomatic Res 2007;63:539-544.
21. Staub F, Bogousslavsky J. Post-stroke depression or fatigue? Eur Neurol 2001;45:3-5.
22. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack. Stroke 2009;40:2276-2293.
23. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-2236.
24. Koella WP. CNS-related (side-)effects of b-blockers with special reference to mechanisms of action. Eur J Clin Pharmacol 1985;28:55-63.
25. Ponchel A, Bombois S, Bordet R, et al. Factors associated with poststroke fatigue: a systematic review. Stroke Res Treat 2015:347920.
26. Duncan F, Kutlubaev MA, Dennis MS, et al. Fatigue after stroke: a systematic review of associations with impaired physical fitness. Int J Stroke 2012;7:157-162.
27. Christensen D, Johnsen SP, Watt T, et al. Dimensions of post-stroke fatigue: a two-year follow-up study. Cerebrovasc Dis 2008;26:134-141.
28. Mead GE, Graham C, Dorman P, et al. Fatigue after stroke: baseline predictors and influence on survival.

analysis of data from uk patients recruited in the international stroke trial. PLoS One 2011;6:e16988.
29. Lewis SJ, Barugh AJ, Greig CA, et al. "Is fatigue after stroke associated with physical deconditioning? A cross-sectional study in ambulatory stroke survivors. Arch Phys Med Rehab 2011;92:295-298.
30. Shaughnessy M, Resnick BM, Macko RF. Testing a model of post-stroke exercise behaviour. Rehabil Nurs 2006;31:15-21.
31. Thilarajah S, Mentiplay BF, Bower KJ, et al. Factors associated with post-stroke physical activity: a systematic review and meta-analysis. Arch Phys Med Rehabil 2017. pii: S0003-9993(17)31264-9.
32. Parks NE, Eskes GA, Gubitz GJ, et al. Fatigue impact scale demonstrates greater fatigue in younger stroke survivors. Can J Neurol Sci 2012;39:619-625.
33. Naess H, Nyland H. Poststroke fatigue and depression are related to mortality in young adults: a cohort study. BMJ Open 2013;3. Article ID 002404.
34. Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. Stroke 2002;33:1327-1333.
35. Wang SS, Wang JJ, Wang PX, et al. Determinants of fatigue after first-ever ischemic stroke during acute phase. PLoS One 2014;9:e110037. Article ID.
36. Tang WK, Liang HJ, Chen YK, et al. Poststroke fatigue is associated with caudate infarcts. J Neurol Sci 2013;324:131-135.
37. Becke K, Kohen R, Lee R, et al. Poststroke fatigue: hints to a biological mechanism. J Stroke Cerebrovasc Dis 2015;24:618-621.
38. Maaijwee NA, Arntz RM, Rutten-Jacobs LC, et al. Post-stroke fatigue and its association with por functional outcome after stroke in young adults. J Neurol Neurosurg Psychiatry 2015;86:o1120-o1126.
39. Duncan F, Lewis SJ, Greig CA, et al. Exploratory longitudinal cohort study of associations of fatigue after stroke. Stroke 2015;46:1052-1058.
40. Wu S, Barugh A, Macleod M, et al. Psychological associations of poststroke fatigue a systematic review and meta-analysis. Stroke 2014;45:1778-1783.
41. van Eijsden HM, van de Port HIM, Visser-Meily JJMA, et al. Poststroke fatigue: who is at risk for an increase in fatigue? Stroke Res Treat 2012. Article ID 863978.
42. Kjörk E, Blomstrand C, Carlsson G, et al. Daily life consequences, cognitive impairment, and fatigue after transient ischemic attack. Acta Neurol Scand 2015. https://doi.org/10.1111/ane.12435.
43. Tang WK, Lu JY, Chen YK, et al. Is fatigue associated with short-term health-related quality of life in stroke. Arch Phys Med Rehabil 2010;91:1511-1515.
44. Vincent-Onabajo G, Adamu A. Impact of poststroke fatigue on health-related quality of life of nigerian stroke survivors. J Stroke 2014;16:195-201. https://doi.org/10.5853/jos.2014.16.3.195.
45. Naess H, Waje-Andreassen U, Thomassen L, et al. Health-related quality of life among young adults with ischemic stroke on long-term follow-up. Stroke 2006;37:1232-1236.