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Timed up-and-go and 2-minute walk test in patients with multiple sclerosis with mild disability: reliability, responsiveness and link with perceived fatigue

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Abstract

BACKGROUND: Mobility limitations are frequent in patients with multiple sclerosis (MS), and could already be present in patients with so-called mild neurological disability (Expanded Disability Status Scale≤4). Assessing mobility in these patients is therefore of paramount importance. Timed up-and-go test (TUG) and 2-minute walk test (2MWT) are two clinically feasible tests which reliability and responsiveness are unknown among these patients. Whether fatigue, which is the number one symptom among these patients, is linked to these limitations remains unknown.

AIM: To explore the intrarater reliability and minimal detectable change (MDC_{95}), as an index of responsiveness, of TUG and 2MWT. To explore their link with perceived fatigue among patients with multiple sclerosis (MS).

DESIGN: Cross-sectional observational study, including two measures.

SETTING: Two university hospital outpatient centers.

POPULATION: Patients (N=63, 49 seen twice) with MS with mild disability (Expanded Disability Status Scale≤4).

METHODS: 2MWT and TUG were performed twice in one occasion and repeated 2 weeks later. Modified fatigue impact scale (MFIS) was used to assess fatigue. Intraclass coefficient correlations were calculated for immediate and 2-week reliability. MDC_{95} were computed. Correlations between mobility indices and fatigue were explored using Spearman's ρ.

RESULTS: Mobility was impaired in comparison to normative values (2MWT: -4.9% from normative distance; TUG: +32% from normative time). The immediate reliability was excellent for both the 2MWT (ICC=0.98) and TUG (ICC=0.98). Reliability at 2 weeks was excellent for 2MWT (ICC=0.95) and very good for TUG (ICC=0.90). MDC_{95} were respectively 20m (2MWT) and 1.3s (TUG). Both measures were significantly weakly correlated to total MFIS (ρ=-0.37 and 0.39, respectively; $p<0.01$).

CONCLUSION: The 2MWT and TUG are highly reliable and responsive in the assessment of respectively the walking capacity and general mobility of patients with MS with mild disability. Mobility impairments are linked to perceived fatigue among these patients.

CLINICAL REHABILITATION IMPACT: TUG and 2MWT are easy to administer and could be reliably used in so called mildly disabled patients with MS to assess mobility limitation.

KEYWORDS: Multiple sclerosis - Mobility - Walking - Psychometric – Fatigue

Introduction

Limitations of mobility are frequent and disabling in patients with multiple sclerosis (MS), with up to 79% of patients reporting moderate or high impact on their quality of life, even when neurological disability is classified as 'mild' (Expanded Disability Status Score (EDSS) ≤4).[1] Evidence showed that gait and balance impairments could be present even in the absence of pyramidal dysfunction.[2] It is therefore noteworthy to assess their mobility. The International Classification of Functioning, Disability and Health, the World Health Organization's framework for measuring health and disability, classifies mobility as an activity (d4), including subcomponents (e.g., walking (d450)).[3]

It is paramount to use high-quality assessment tools to subtly monitor disease progression, to identify patients needing rehabilitation and to guide and monitor the efficacy of treatments among patients with apparently mild disability, both in research and clinical routine. Reliability and responsiveness are crucial determinants of the quality of these tools, and could be influenced by the measurement tools themselves, and the characteristics of the population submitted to the test (e.g., fatigability, cognitive impairments, motivation and so on).[4]

Two simple tests are widely used in clinical practice to assess distinct aspects of mobility: the timed up-and-go test (TUG)[5] assesses the general ability to move around (d450-d469 in the ICF classification), while the 2-minute walk test (2MWT)[6] specifically assesses the walking capacity on short distances (d4500). While their feasibility and validity have been demonstrated among pwMS with mild disability[6,7], data on their reliability and responsiveness are lacking among these patients.

Fatigue is also a highly prevalent and disabling symptom among those patients, sometimes preceding the clinically objectified impairments.[8] Within the ICF classification,

fatigue is an impairment of the energy and drive functions (b130). The modified fatigue impact scale (MFIS) is a 21-item questionnaire, including 3 subscales assessing cognitive (MFIScog), physical (MFISphy) and psychosocial (MFISpsychosoc) fatigue, that has been validated in people with MS (pwMS). Higher scores indicate higher fatigue, and the maximal total score (MFIStot) is 84. A cutoff of 38 has been proposed to identify fatigued patients.[9] Whether perceived fatigue is linked to limitations of mobility in mildly disabled patients remains unknown.

We aimed to study the immediate and middle-term reliability of the TUG and the 2MWT among patients suffering from MS with so-called mild neurological disability (EDSS≤4), and their minimal detectable change (MDC_{95}), as an index of responsiveness. We also explored whether mobility was linked to perceived fatigue, as assessed by the MFIS, among these patients.

Methods

Guidelines for reporting reliability and agreement studies (GRRAS) were followed for reporting the psychometric phase of this study.[10]

For this multicentered cross-sectional study, a convenience sample of consecutive patients was recruited from the MS consultation at the Department of Neurology of the Cliniques universitaires Saint-Luc (Bruxelles, Belgium), and the Department of Neurology of the UCL Namur, site Godinne (Godinne, Belgium), between December 2015 and March 2018. Inclusion criteria included a diagnosis of MS, according to the McDonald criteria[11], an EDSS score≤4 and an age between 18 and 65 years. Patients were not included if they had other pathologies limiting their mobility (e.g., orthopedic, rheumatologic or other neurological conditions) or had, during the preceding 3 months, either a relapse or a change in their disease-modifying treatment. Patients were given two appointments (A and B), two weeks

apart (range: 11 to 17 days), for two similar evaluations. Patients received no rehabilitation intervention and were excluded from the sample if they experienced a relapse, or other serious health issue between the appointments. This study was approved by the relevant ethics committee and all patients signed a written informed consent.

TUG was performed according to recommendations.[5] In brief, patients were seated in a non-armed chair and were asked to sit-up, walk three meter, turn around a cone, walk back and sit back in the chair. They were asked to do it as fast as possible, without running. The score is the time taken by the patient to perform that task. The 2MWT was performed in a 30-meter hallway, marked every 2 meters. Patients were instructed to do as much back and forth as possible in 2 minutes, without running. The assessor followed the patient by about 1 meter and notified the patient after 1 minute. The distance covered during these 2 minutes is the considered outcome. Two trained researchers (MV and MD) from the same team performed the assessments. Each patient was evaluated by the same single assessor. Each evaluation comprised two repetitions (A_1 and A_2 at time A, B_1 and B_2 at time B) of a 2MWT, separated by a 5-minute seated rest, and two repetitions of a TUG, separated by a 1-minute seated rest. The 2MWT and the TUG were separated by a 10-minute seated rest, during which the patient fulfilled the MFIS. Tests were performed according to standardized protocols[5, 12], and the general protocol was set up to avoid fatigue effects. Average of the two trials performed a same day were also considered (A_{mean} and B_{mean}).

Data normality was checked through the Kolmogorov-Smirnov test. Z-scores were computed for 2MWT, based on published normative values[13]. Regarding the TUG, normative values were only available for women, and SD were narrow[14]; therefore, deviation from the norm, expressed as a percentage, were computed, rather than Z-scores. Intraclass correlation coefficients (ICC) (two-way random model, absolute agreement) were used to assess immediate (A_1-A_2) and middle-term (A_{mean}-B_{mean} and A_1-B_1) reliability. Bland-Altman

method, including paired t-test, was used to compute agreement between measures. MDC_{95} represents the magnitude of the change between two measures, necessary to exceed the error of measurement, with a confidence interval of 95%. It was calculated as follows:

$$MDC_{95} = 1.96 \times \sqrt{2} \times SEM$$ (SEM=Standard error of measurement).

Correlations between normalized mobility scores and MFIS, and its subcomponents, were studied using Spearman's ρ. Data collected at time A was used for these analyses. Observed power was higher than 80%.

Sensitivity analysis were conducted to ensure the stability of our results. Analyses were reperformed for each center taken separately and for data gathered either before or after January 2018.

Results

Sixty-three patients (49 women, mean age: 43±9 years, median disease duration 8 [5-14] years, median EDSS 2 [1.25-3]) were assessed at time A by the two trained raters. Among these, 49 patients were reassessed at time B. The MFIS missed for 3 out of these 49 patients. All continuous data were normally distributed, apart from disease duration. Table I summarizes demographic data. The overall mean (n=63) of the 2MWT was 179±32 m (range: 108.5-239m) and of the TUG, 7.7±1.70s (range: 5.0-12.5s). In comparison to normative values, patients covered, in average, 4.9% (10.1m, $p<0.05$) less distance during the 2MWT, and women took 32% (1.9s, $p<0.05$) longer to perform the TUG. Table II summarizes test-related data.

Regarding the 2MWT, immediate reliability (A_1 and A_2) was excellent (ICC=0.98). At middle term, reliability was excellent, both for the means (A_{mean} and B_{mean}) and the first trials (A_1 and B_1) considered alone (ICC=0.95 for both). Overall, no learning effect was observed at

short-term, while a significant mean improvement of 5.6m (3%) was observed at two weeks. The MDC_{95} was 20m, considering the first trials only (A_1-B_1).

The immediate reliability (A_1 and A_2) of the TUG was excellent (ICC=0.98). The reliability at middle term was very good, and better for the mean of the two trials (A_{mean}-B_{mean}) than for first trials alone (A_1-B_1) (ICC=0.90 and 0.86, respectively). No learning effect was detected. The MDC_{95} was calculated as 1.3s, considering the mean of two trials (A_{mean}-B_{mean}). Agreements between the mobility tests trials are illustrated in Figure 1.

Data for MFIS missed for one patient at time A (n=62) and two patients at time B (n=47). Median MFIStot score was 50 (IQR: 33.25-61.5) at time A and 47.5 at time B (IQR: 33.75-57.25). According to the cutoff, 65% (n=40) and 72% (n=34) of the patients were reportedly highly fatigued, at time A and B respectively. Two-week reliability of the MFIS was very good for total score (ICC=0.90) and cognitive (ICC=0.89) and physical (ICC=0.89) subscales and good for psychosocial (ICC=0.73) subscales.

2MWT was negatively correlated with MFIStot and its subscales, while TUG was positively correlated. Correlations of both tests with MFIStot and MFISphy were low ($0.30<\rho<0.50$, $p<0.01$), while correlations with MFISpsychosoc were moderate ($0.50<\rho<0.70$, $p<0.001$). Correlations between the mobility tests and MFIScog were statistically significant, but negligible in size ($\rho<0.30$, $p<0.05$). Correlations were similar between for times A and B. Correlations values are reported in Table III and illustrated in Figure 2.

Results from the sensitivity analyses performed with partial data (from one center only or excluding any time range) were not materially different from those presented.

Discussion

Patients with MS and an EDSS≤4 showed worse functional mobility and walking capacity, in comparison to normative values. We observed excellent reliability, both at short

and middle-term, for the 2MWT and the TUG. Meanwhile, their MDC_{95} showed that these tests are sufficiently responsive to be used in this clinical population. The French version of the MFIS is also highly reliable, as well as its physical and cognitive subscales. Furthermore, among these so-called mildly disables pwMS, functional mobility and walking capacity are moderately linked to perceived fatigue.

An excellent reliability at two weeks has been previously demonstrated for the 2MWT and the TUG among pwMS with more severe disability (EDSS 2 to 6.5; respectively, ICC= 0.97 and 0.96 for TUG and 2MWT).[15] For the 2MWT, the MDC_{95} was excellent, with a change of 20m (11%) being detectable, when considering the first trial only (equal as when using the mean of two trials), suggesting that a single trial of the 2MWT is sufficient. Interestingly, this value is relatively equal to the MDC_{95} of the six-minute walk test (55m).[16] However, at two weeks, a slight learning effect of 5.6m was present. A similar small learning effect (4.4m) has been described in healthy subjects.[13] However, it is not known whether this learning effect will last ~~further~~ longer than 2 weeks. Given that the MDC_{95} is 20m and that there is a systematic learning effect of 5m, at two weeks, a decline of 15m or more, or an improvement of 25m or more should be considered significant, among a given patient.

Regarding TUG, the immediate and middle-term reliability are excellent, with no learning effect observed. The reliability and agreement are slightly better when considering the mean of two consecutive measures, in comparison to a single measure, supporting the use of the mean of two consecutive trials for this test. A change of 1.32s (17%) is considered a true change. This constitute an acceptable reliability and responsiveness, similar or better that what was found in other populations of patients with neurological disorders.[17, 18]

Other versions of the MFIS has been previously shown to be reliable, but it has never been shown for the French version.[19] We found that the French version of MFIStot and its physical and cognitive subscales were also highly reliable at 2 weeks. The psychosocial

subscale, involving only two item, appeared to be less reliable, and should therefore cautiously used independently.

A significant negative association was found between perceived fatigue and mobility capacity. Such an association has been recently shown by Dalgas et al., however, they used raw scores, as we used age- and sex-normalized results.[20] Furthermore, while they included a large spectrum of pwMS (with so-called mild and moderate disability), we specifically focused on patients that are allegedly not limited, or limited over 500 m, in their walking capacity. Gijbels et al. have also shown low significant correlations between 2MWT and 6-minute walk test, and MFISphy (r=-0.31 and -0.29, respectively).[6] Our findings indicate that, in pwMS and so-called mild disability, mobility limitations are linked to perceived fatigue. A cause-consequence relationship cannot be inferred based on our results. However, as impaired central activation has been linked to perceived fatigue in theses patients[21], one could speculate that the precocious damage of common central neural pathways could lead to both phenomenon, but this hypothesis needs to be confirmed by longitudinal studies.

Several limitations of our study should be acknowledged. First, our sample size is conveniently determined, and not based on a statistical calculation. Nevertheless, data were normally distributed, and a power superior to 80% was obtained for most of our analysis. Furthermore, sensitivity analysis did not change our findings. In addition, we used only one fatigue scale, and the use of the Fatigue Severity Scale, most frequently used in the literature, could have enriched our study. However, this scale has a significant ceiling effect.[22] Finally, the lack of normative values for TUG among men precludes the study of normalized scores in the complete population. Strengths of our work include the use of Z-scores, allowing to compare with a reference population and a sex- and age-based normalization when studying the correlations with fatigue. In addition, we focused on patients with mild neurological

disability, among whom that allow us to establish reliability and responsiveness for this specific, clinically relevant population.

Conclusions

Walking capacity and functional mobility are impaired in pwMS and mild disability and could be reliably assessed by two tests, respectively the 2MWT and the TUG. These tests are easy to use in a clinical setting. They should therefore be routinely used to monitor disease progression and/or treatment response in so-called mildly disabled pwMS. Furthermore, mobility limitations are related to fatigue among these patients.

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Conflict of interest statement. - The authors declare that they have no conflict of interest.

Supplementary material. - Detailed methods and results could be accessed by sending an e-mail to the corresponding author (maxime.valet@uclouvain.be).

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TABLES

Table I. Demographic data.

Women/Men, n (%)	49/14 (78%/22%)
Clinical Course, n (%)	
Relapsing-Remitting	57 (90%)
Primary Progressive	5 (9%)
Secondary Progressive	1 (1%)
EDSS	2 [1.25-3]
Age (years)	43 ± 9
Disease duration (years)	8 [5-14]

Demographic and test-related data at time A. Results are expressed as mean ± SD or median [Interquartile range]. EDSS: expanded disability status scale. 2MWT: two-minute walk test. TUG: timed up-and-go test.

Table II. Test-related data.

MOBILITY TEST	***A*$_1$**	***A2***	***A*$_{mean}$**	***B1***	***B2***	***B*$_{mean}$**
	(n=63)	***(n=63)***	***(n=63)***	***(n=49)***	***(n=49)***	***(n=49)***
2MWT (m)	175 ± 33	177 ± 34	176 ± 33	181 ± 32	182 ± 34	182 ± 33
2MWT (% of the norm)		104.9 ± 17.7				
2MWT (Z-scores)		-0.29 ± 1.08				
TUG (s)	7.8 ± 1.71	7.7 ± 1.74	7.8 ± 1.72	7.5 ± 1.58	7.5 ± 1.62	7.5 ± 1.60
TUG (% of the norm)			131.8 ± 28			
FATIGUE	***A1***	***A2***	***A*$_{mean}$**	***B1***	***B2***	***B*$_{mean}$**
QUESTIONNAIRE	***(n=62)***	***(n=62)***	***(n=62)***	***(n=46)***	***(n=46)***	***(n=46)***
MFIScog			23.5 [10.75-28]			22 [14–26.25]
MFISphy			23 [17-27.5]			23 [13.25-26.25]
MFISpsychosoc			4 [2-6]			4 [2-5]
MFIStot			50 [33-62.75]			47.5 [30.75-58.25]

Results are expressed as mean ± SD or median [Interquartile range]. MFIScog: modified fatigue impact scale, cognitive subscale. MFISphy: modified fatigue impact scale, physical subscale. MFISpsychosoc: modified fatigue impact scale, psychosocial subscale. MFIStot: modified fatigue impact scale, total score.

Table III. Spearman's correlations between fatigue and mobility scores.

	MFIScog	*MFISphy*	*MFISpsychos*	*MFIStot*
EDSS	0.31*	0.29*	0.38**	0.33**
2MWT	-0.28*	-0.37**	-0.52**	-0.37**
TUG	0.30*	0.39**	0.55**	0.39**

MFIS: modified fatigue impact scale (Cog: cognitive subscale, Phy: physical subscale, Psychosoc: psychosocial subscale), 2MWT: 2-minute walk test (expressed as Z-scores), TUG: timed up-and-go test (expressed as the difference with normative values, in percentage).

Correlations are calculated from data collected at time A (n=62). Only women are included for TUG (n=47).

* $p<0.05$, ** $p<0.01$

TITLES OF FIGURES

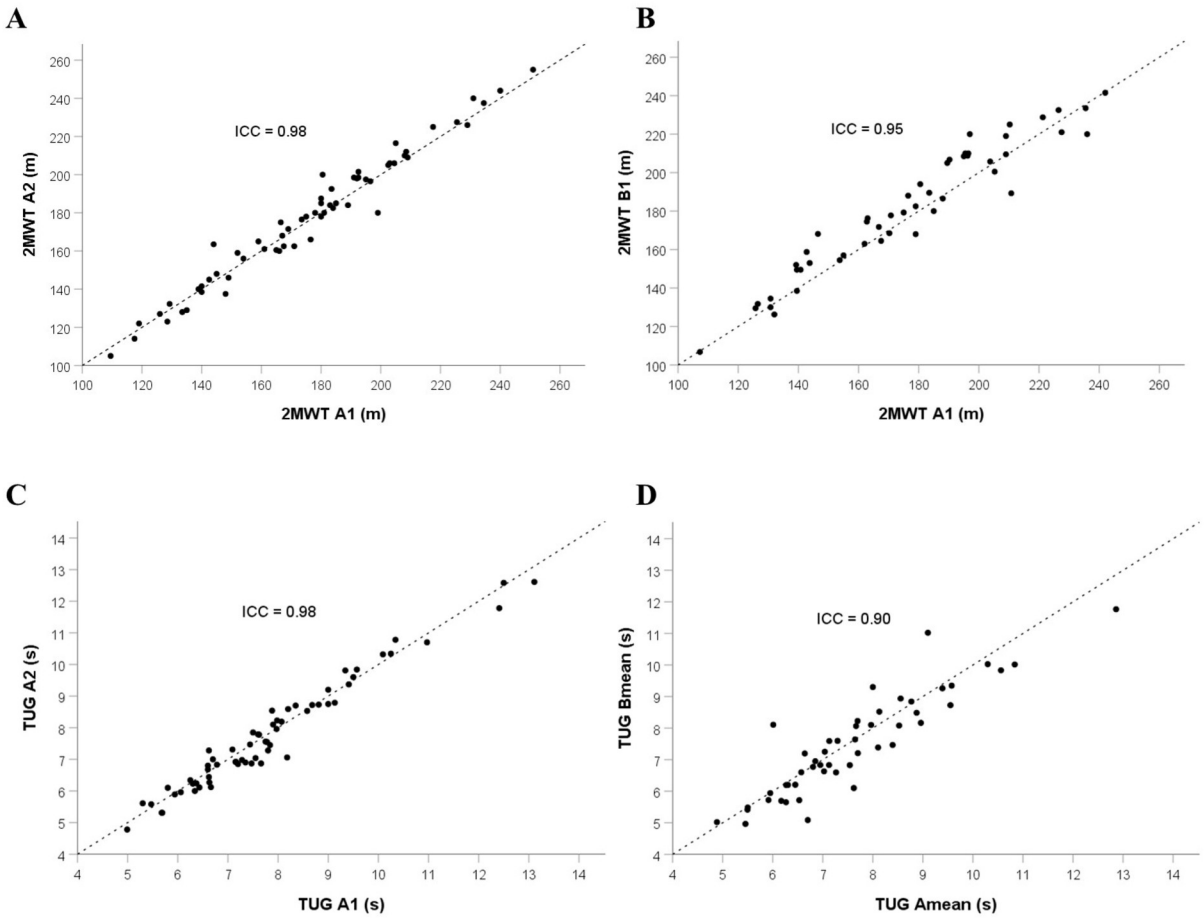
Figure 1. – Scatter plots showing the immediate (panel A and C) and middle-term (panel B and D) reliability of the two-minute walk (panel A and B) test and the timed up-and-go test (panel C and D). The dotted lines indicate the equivalence between the tests.

2MWT: two-minute walk test; TUG: timed up-and-go test; ICC: intraclass correlation coefficient; A: first evaluation; B: second evaluation, 2 weeks later; A1: first trial of the first evaluation; A2: second trial of the first evaluation.

Figure 2. – Relations between perceived fatigue and normalized mobility scores.

2MWT A1: two-minute walk test at time A1. TUG Amean: timed up-and-go test at time A (mean of the two trials). MFIStot A: modified fatigue impact scale, total score, at time A.

Vertical dotted-lines indicate the cut-off for pathological fatigue. Horizontal dotted-lines indicate mean normative values (Z-score=0).



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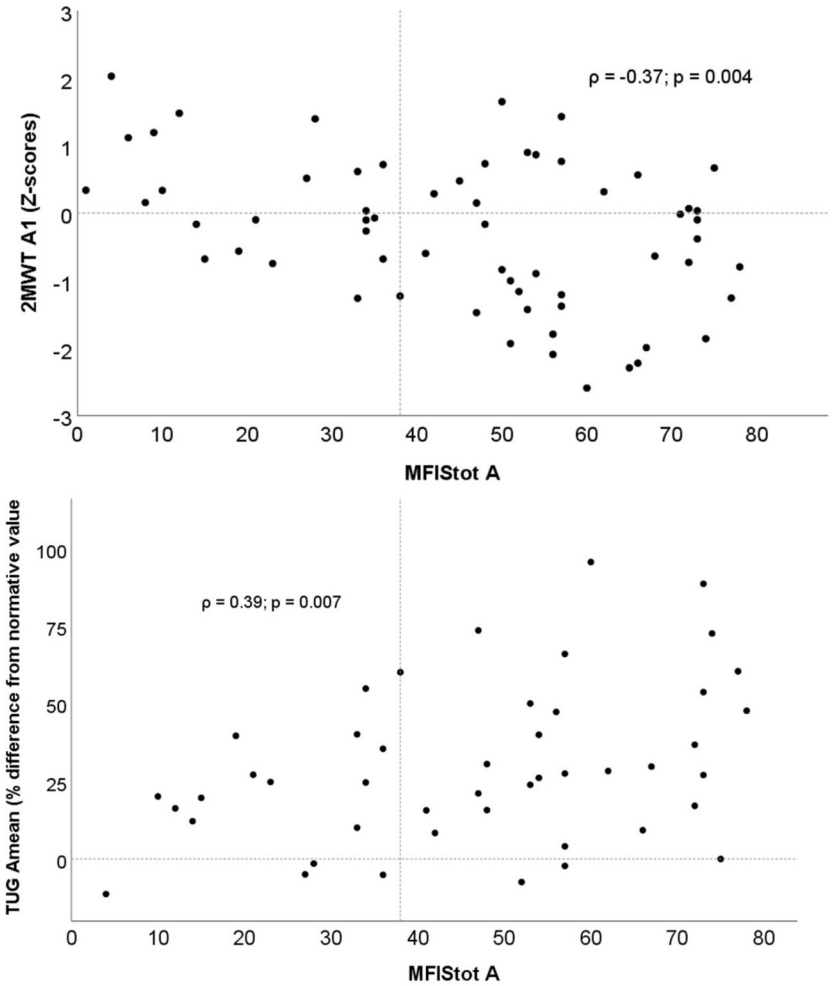

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