Acta Scientific Neurology (ISSN: 2582-1121)

Volume 6 Issue 7 July 2023

Research Article

Index of Overall Disability due to Multiple Sclerosis

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Received: May 05, 2023

Published: June 03, 2023

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Abstract

Background: Existing tests to assess disabilities due to functional deficits in Multiple sclerosis (MS) differ in number of items, number of response-categories, domains covered, scoring systems, etc. and are not comparable.

Objective: The paper proposes two methods to convert discrete raw scores of items/domains of MS tests to continuous scores following normal distribution satisfying desired properties and facilitating meaningful comparisons, assessment of progress/deterioration, parametric statistical analysis and symmetric equivalent-scores for better comparisons and integration of MS tests.

Methods: Ordinal raw scores are converted to equidistant scores by weighted sum followed by linear transformations (Method 1) and alternate method of scoring health-state-profiles in 5-Domain 5-Level set up (Method 2). Proposed equivalent-scores having equal areas under normal curve help to derive meaningful cut-off scores, equivalent boundary points of the classes and integration of MS tests

Results: Proposed scores under each method help in computation of total score reflecting total disorder by overall index of disability in MS, with the same score range of items satisfy desired properties of measurement including meaningful arithmetic aggregations, minimization of tied scores. Domain scores and test scores follow normal and facilitate better ranking, comparisons, quantify changes from longitudinal data, and parametric statistical analysis, computation of reliability, validity, etc. Symmetric equivalent scores avoid conversion tables generated from the Crosswalk Studies which may vary by several points and may not provide inverse function for each score. The Method 2 indicates domain-wise status of a patient and helps practitioners to decide priorities and course of action accordingly. However, Method 2 requires significant modifications of existing tests to fit 5D-5L set up.

Conclusions: Considering theoretical advantages including meaningfulness of operations, easy comprehension, better comparisons, Method 1 is recommended with the suggestion to report test score and also domain scores.

Keywords: Multiple Sclerosis, Cognitive Tests; Normal Distribution; Equivalent Scores; Reliability; Responsiveness

Introduction

Multiple sclerosis (MS) can be described as a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS), characterized by occurrence of relapsing neurological deficits affecting different functional system (FS) of CNS. Numbers of instruments are there to assess clinical severity and functional deficits in MS. The 20-point Expanded Disability Status Scale (EDSS) score ranges between zero (indicating "Normal") to 10 (death by MS) with 0.5 point steps, combining intermediate scores on eight FS-scales to measure progression of MS. FS contains eight scales on different functions of CNS, using 6-point, 5-point items and a binary item (0: none, 1: other neurological findings attributed to MS). A score of one in FS indicates that the patient is not aware of the deficit and that the deficit does not interfere with normal daily activities, except for Visual, Bowel/Bladder and Cerebral FS. Multiple outcome measures and MS specific Patient-reported outcome measures (PROMs) are also used to assess disease severity, where total score = sum

of domain scores assuming equal importance to the domains [1]. For example, the Guy's neurological disability scale (GNDS) with 12 functional domains (categories) is a PROM in MS where total score (from 0 to 60) is obtained as sum of domain scores ranging between 0 to 5 and higher score implies more disability.

Comparison of EDSS with MSQOL-54 (MS specific instrument) reveled moderate level of overlapping [2]. Tests to assess severity of MS differ with respect to length (number of items), width (number of response-categories/levels), sub-classes/domains covered, scoring systems, etc. and are not comparable.

Brief International Cognitive Assessment for MS (BICAMS) [3] is a neuropsychological battery containing three tests viz. California Verbal Learning Test to measure learning and verbal memory, Brief Visuospatial Memory Test and the Symbol Digit Modalities Test (SDMT) to measure attention and information processing speed and generates cardinal scores. However, normalization data for SDMT are complicated since interpretive error of normative raw test scores in groups with different cultures/languages/countries could be different. A score of Z_0= population mean minus 1.5 SD in BICAMS battery is taken to be impaired.

Another scoring system considering change in assessment was proposed [4] redefining and calculating the brain functions FS in EDSS by $EDSS_{Basal}$ and $EDSS_{Modified}$ using the scores obtained in the BICAMS [5]. However, $EDSS_{Basal}$ and $EDSS_{Modified}$ follow different distributions and comparison by *t*-statistics is unjustified.

Eight independent FS dimensions cannot be summed [6]. Moreover, summative scores of ordinal scales are not appropriate [7]. Suggestions of modifying gait assessment criteria and redefining each FS do not propose a homogeneous assessment criterion [8]. A single clinical outcome measure of disease progression or integration of outcome measures reflecting various stages of MS was preferred [9].

Test score of MS disabilities giving equal importance to the domains ignores domain-wise status of patients. Health-state-profiles showing assessed health in each domain help practitioners to focus on domains and decide priorities and course of action. In line with EuroQol five-dimensional scales *(EQ-5D-5L)* (https://euroqol.org/eq-5d-instruments/sample-demo/) health-state-profile of a patient can be indicated by a categorical score with a 5-digited number like 1-2-3-4-5 or a permutation of the digits 1 to 5 where repetitions are allowed. However, it requires consensus on the domains and standardization of scoring system by *5*-point items (1 to 5) for each domain.

The paper proposes two methods to convert discrete raw scores of items/domains to continuous scores following normal distribution to facilitate meaningful comparisons, assessment of progress/deterioration, parametric statistical analysis and symmetric equivalent-scores for better comparisons and integration of MS tests.

Literature Survey

The Task Force of the National Sclerosis Society proposed quantitative functional measures to be combined into a single cardinal score [10]. Adding cardinal scores with ordinal scores of EDSS, FS, PROMs, etc. are problematic.

Disease severity are measured by objective measures (like clinical outcome measures, non-clinical outcome measures, MRI) or subjective measures like MS-related PROMs [11], general health-status [12], MS symptoms [13], quality-of-life measures [14-15]. Assessing MS progression by vision, strength, coordination, cognition, fatigue, daily activities etc. was suggested [9].

MS-relapses could be an outcome measure, since number of relapse decreases as patients' progress with time [16]. However, number of MS-relapses and severity of relapses are different concepts. Rate of progression on the relapses, has uncertain utility since relapses showed no reliable impact on EDSS progression [17]. Association between MS-relapse and long-term disability is weak to moderate [18], despite clear association between MS-relapse-rate and changes in both the EDSS and MSFC over time [9].

EDSS has been criticized for its limitations [19-20]. Major limitations are

- Assessment of cognitive ability is ambiguous and lacks sensitivity [5]
- Non-comparable scores since transition from EDSS 1 to 2 is different from 6 to 7. Thus, the scale is non-linear. Rate of progression on EDSS depends on EDSS level at trial entry.
- Typical distribution of EDSS scores shows two modes (bimodal).

- Poor responsiveness especially at lower and higher range of EDSS [21-22]
- Clinical interpretations of change in EDSS are different at different score-levels and require further investigation using functional scales [20]. Time required to increase EDSS from 0 to 1.5 (applicable if ambulation is "unrestricted") is similar to increase from 3.5 to 4 (Time from 0-1 + Time from 1-1.5 = 3.3 years vs. Time from 3.5-4 = 4.2 years) [23]. Thus, time to an increase of EDSS by 1.5-point starting with zero EDSS, corresponds to the time to a smaller EDSS.

Improved quality of FS requires clearer definitions of different FSs avoiding intra-observer and inter-observer variability, standardization of brain function FS assessment [5]. Norming the MS tests and standardization of raw scores or transformed scores satisfying desired properties are needed for Clinical Judgments on patient's MS-profile. Equivalent Scores offer a solution in this respect to derive meaningful cut-off scores.

Other Problem areas

- Addition of ordinal scores is not meaningful since response-categories are not equidistant [24-25]
- Summative scores ignores the pattern of obtaining such scores and often results in tied scores implying poor discriminating value of the test. Consider the following hypothetical example of 10 individuals, each with total score of 11as given in table 1.

Sl.No.	Visual functions (5-point; 0 to 4)	Hearing Loss (5-point; 0 to 4)	Pyramidal functions (6-point; 0 to 5)	Extraocular movements impairment (5-point; 0 to 4)	Overall motor functions (4-point; 0 to 3)	Total
1	2	2	3	2	2	11
2	0	3	5	2	1	11
3	4	4	1	1	1	11
4	3	3	3	1	1	11
5	1	1	3	3	3	11
6	0	1	3	4	3	11
7	0	1	4	4	2	11
8	0	1	3	3	3	11
9	0	1	5	3	2	11
10	0	1	4	4	2	11
Total	10	18	34	28	20	110
Mean	1.0	1.8	3.4	2.8	2.0	11.0
Variance	2.0	1.16	1.24	1.36	0.6	0.0

Table 1: Tied Scores.

Observations

- The test failed to discriminate among the individuals
- Domains contributed differently to total scores. Mean score of Pyramidal functions measured in 6-point scale was highest. Thus, equal importance to the domains given by a battery is not justified.
- The individuals formed homogeneous sub-group in terms of total scores but not in terms of domain scores and variance of domains varied.
- Zero scores artificially lower mean and variance of domain/test scores. Alternatives could be marked as 1, 2, 3, 4, 5, etc. avoiding zeros i.e., a linear transformation of the anchor values, without changing the data structure.

Tests do not consider distribution of scores. Interpretations of X ± Y require finding the joint distribution of X ± Y. But, distributions of item scores are unknown and different.

$X + Y = Z$ is most meaningful if $P(Z = z) = P$ (X = x, Y = z-x) for discrete case and $P(Z \leq z) = P(X + Y \leq z) = \int_{-\infty}^{\infty}(\int_{-\infty}^{z} f_{X,Y}(x, t-x)dt)\,dx$ for continuous case. Thus, it is necessary to know probability density function (pdf) of X and Y and their convolution.

- Bias and uncertainty tends to increase with ceiling and floor effects and affect estimate of group difference, and decisions of the equivalence testing methods [26].
- Total score of FS indicating total disorder is not available, despite need of overall index of disability for studies in MS.
- Statistics like t-test, ANOVA, Factor analysis (FA), Principal component analysis (PCA), etc. assume normally distributed data. Verification of normality is rarely undertaken.
- Cronbach's alpha assumes one-dimensional scale and is not valid for scales/batteries measuring multi-factors. Despite finding four independent factors of GNDS [27], Cronbach's alpha = 0.79 was computed [1].
- Validity as correlation with criterion variable reflects validity of the criterion variable also.

- Finding equivalent scores by regression, equipercentile scores have limitations. Equating is not forecasting and equating method must be different from forecasting methods [28]. Percentile scores ranging between 1to 99 are not of equal-interval and not additive. Distance between 15-th and 25-th percentile distance between 45-th and 55-th percentile. If P_i denotes the i-th percentile score and if frequency for the interval corresponding to P_i is zero, then $P_i \not> P_{(i-1)}$. Equivalent score by equipercentile approach is a function $f: X \to Y$ with no inverse i.e. there is no function $f^{-1}: Y \to X$. Sensitivity of X-scores and Y-score may be different.

Proposed method

Method 1

Transform item raw scores (X) → Equidistant scores (E) → Standardized scores(Z) → P-scores following Normal in the range [1, 100], irrespective of length and width of scales by following stages [29]

- X → E: Take weighted sum by assigning different weights to response-categories of different items so that for a 5-point (say) item, $W_1, 2W_2, 3W_3, 4W_4, 5W_5$ forms a monotonic Arithmetic Progression where $5W_5 > 4W_4 > 3W_3 > 2W_2 > W_1$
- Standardize E-scores of an item to

$$Z = \frac{E-\bar{E}}{SD(E)} \sim N(0,1) \qquad \text{----------(1)}$$

- Convert Z-scores to proposed scores by

$$P = (99)\left[\frac{Z_{ij}-Min_{Z_{ij}}}{Max_{Z_{ij}}-Min_{Z_{ij}}}\right] + 1 \qquad \text{----------(2)}$$

For items generating cardinal scores like cognitive tests used in Neuropsychology, Raw scores of items (X) can be standardized as $Z = \frac{X-\bar{X}}{SD(X)} \sim N(0,1)$ avoiding the stage I.

Method 2

Single score of health-state-profile emerging from EuroQol five-dimensional questionnaires was proposed [30]. Consider a questionnaire with 5 domains, each having 5 levels marked as 1 to 5 has been administered to n-persons where $f_{ij} > 0$ denotes frequency of the j-th level (response-category) of the i-th domain. Take weight to j-th level of i-th domain as $p_{ij} = \frac{f_{ij}}{n}$ for $i, j = 1, 2, 3, 4, 5$. Express health-state-profile 1-2-3-4-5 of i-th person as an expected value $Y_{i,5L} = 1(p_{11}) + 2(p_{22}) + 3(p_{33}) + 4(p_{44}) + 5(p_{55})$ which is different from 5-4-3-2-1= $5(p_{11}) + 4(p_{22}) + 3(p_{33}) + 2(p_{44}) + 1(p_{55})$.

Y_{5L} for the minimum profile 1-1-1-1-1= $\sum_{i=1}^{5} p_{i1}$ and for the maximum profile 5-5-5-5-5 = $5\sum_{i=1}^{5} p_{i5}$. Clearly, $Y_{i,5L}$ is additive since $E(X + Y) = E(X) + E(Y)$ as persons and Y are independent. It is possible to find mean, variance of and correlations matrix of domains for a sample. Repeat Stage II and III to standardize Y_{5L} by $Z_i = \frac{Y_{i,5L}-\bar{Y}_{5L}}{SD(Y_{5L})}$ and transform Z_i to proposed score in the score range [1,100] by equation (2).

In each method, the proposed scores (P) following normal distribution avoids negative values and reflects intensity of MS by continuous variable. Domain/Sub-scale score as sum of normally distributed item-wise P-scores and test score as sum of domain scores also follows normal, parameters of which can be obtained from data. If $X \sim N(\mu_X, \sigma_X^2)$ and $Y \sim N(\mu_Y, \sigma_Y^2)$ then $X + Y \sim N(\mu_X + \mu_Y, \sigma_X^2 + \sigma_X^2 + 2\sigma_{X,Y})$. Normality provides meaningful arithmetic aggregation, enables finding sample mean and SD of a group of patients, estimating population mean (μ), population variance (σ_P^2) and confidence interval of and testing hypothesis: $H_0: \mu_1 = \mu_2$ for two populations or one population across time.

Other Advantages of P-scores

- Enables calculation of all descriptive statistics and undertaking analysis under parametric set-up.
- Provides unique ranks to individuals.

- Rejection of H_0: $\mu_{P_{pre-group}} = \mu_{P_{post-group}}$ implies treatments/ cares are effective. Testing of the requires paired *t*-tests since pre-treatment group and post-treatment group are not independent.
- Assess progress/deterioration of cognitive ability by $\frac{P_{it}-P_{i(t-1)}}{P_{i(t-1)}} \times 100$ where P_{it} denotes *P*-score of the *i*-th patient at *t*-th time period. The ratio indicates responsiveness of the scale and reflects effectiveness of a treatment plan by assessing even small improvement of cognitive abilities. Assuming higher test score implies higher impairments and higher MS severity, $\frac{P_{it}-P_{i(t-1)}}{P_{i(t-1)}} \times 100 > 0 \Longrightarrow P_{it} > P_{i(t-1)} \Longrightarrow$ Deterioration of cognitive ability of the *i*-th patient at *t*-th period against the previous period requiring a relook to the treatment plan for the patient. Similarly, $\bar{P}_t > \overline{P_{(t-1)}}$ indicates deterioration of cognitive ability for the group in the *t*-th period over *(t-1)*-th period and thus, require immediate action. $SD\ (P_t) > SD\ (P_{t-1})$ indicates intensity of the sample at the *t*-th period was more heterogeneous than the previous period.
- The graph of $\frac{P_{it}-P_{i(t-1)}}{P_{i(t-1)}} \times 100$ across time may reflect survival function in terms of progress or decline of cognitive abilities.
- Reliability of *i*-th domain () can be found as correlation between the domain scores and total scores (analogous to item-total correlation). Avoiding uni-dimensionality assumption of Cronbach alpha, test/battery reliability (considering domain reliabilities was proposed [31] as
- $r_{tt} = \frac{\sum_{i=1}^{5} r_{tt(i)} S_{Xi} + \sum_{i=1, i\neq jk}^{5} \sum_{j=1}^{5} 2COV(X_i, X_j)}{\sum_{i=1}^{5} S_{Xi} + \sum_{i=1, i\neq jk}^{5} \sum_{j=1}^{5} 2COV(X_i, X_j)}$ ----------(3)
- where denotes sample SD of the *i*-th domain
- Population estimates of item variance and test variance help to compute Cronbach's alpha at population level as
- $\hat{\alpha} = (\frac{n}{n-1})\ (1 - \frac{Sum\ of\ estimates\ of\ variance\ of\ items/domains\ )}{Estimate\ of\ test\ variance})$ ----------(4)
- Normally distributed scores enables undertaking of PCA and find factorial validity as
- $Validity_{Factorial} = \frac{\lambda_1}{\Sigma \lambda_i}$ ----------(5)
- Where denotes highest eigenvalue corresponding to the first principal component, reflecting the main factor for which the test was developed. Such factorial validity avoids the problems of construct validity and selection of criterion scale [32].

Equivalent scores

P-score in test-1 is equivalent to *P*-score in test-2 ($X_0 \Leftrightarrow Y_0$) if X_0 and Y_0 ensure same relative position in the sample i.e. area under the curve showing distribution of test-1 up to X_0 = area of the same for test-2 up to Y_0 i.e.

$$\int_{-\infty}^{X_0} f(x)dx = \int_{-\infty}^{Y_0} g(y)dy \quad \text{----------(6)}$$

where f *(X)* and g*(Y)* denote normal pdf of test-1 following N (μ_1, σ_1^2) and test-2 following N (μ_2, σ_2^2) respectively. Equation (6) ensures symmetric equating; same score ranges and can be solved using Standard Normal probability table.

Illustration of solution of (6)

Suppose $X \sim N(33.75803, 10.74164^2)$; $Y \sim N(64.78584, 20.94855^2)$ and $X_0 = 25.5947$.

Here, $Z_{X0} = \frac{25.5947-33.75803}{10.74164}$ = (-) 0.75997 and

$\int_{-\infty}^{X_0} f(x)dx =$ Area under $N(0,1)$up to$(-)0.75997$

= 0.5 - Area under $N(0,1)$ between zero and 0.75997 = 0.2236

Similarly, $Z_{Y0} = \frac{Y_0-64.78584}{20.94855}$ So, $\int_{-\infty}^{Y_0} g(y)dy = \int_{-\infty}^{Z_{Y0}} Zdz$

If X_0 is equivalent to Y_0, then $0.2236 = \int_{-\infty}^{\frac{Y_0-64.78584}{20.94855}} Zdz$

$\Longrightarrow 0.2236 = 0.5 - \int_{0}^{\frac{Y_0-64.78584}{20.94855}} Zdz \Longrightarrow 0.2764 = \int_{0}^{\frac{Y_0-64.78584}{20.94855}} Zdz$

From Standard Normal probability table, area of 0.2764 under *N (0.1)* at the right of mean is 0.76. Thus, $\frac{Y_0-64.78584}{20.94855} = 0.76 \Longrightarrow Y_0$ 80.70773 implying 25.5947 in test-1 and 80.70773 in test-2 are equivalent. Clearly, $X_0 \Leftrightarrow Y_0$ imply $Y_0 \Leftrightarrow X_0$ i.e. equating is symmetric and hence interchangeable. Thus, equivalent scores of the tests with different formats can be used for assessing disease severity and classification of individuals with equivalent boundary points of the classes like Normal, Mild MS, Moderate MS and Severe MS or overall status as Stable, Improved, Worsened. Equivalent scores by (6) permit integration of various tests [33] and correlation between such equivalent scores was over 0.99.

Among various methods of classification, Quartile clustering merits consideration for easy interpretation and distinct semantics [34]. Quartile clustering of $P \sim N(\mu, \sigma^2)$ gives well-defined cut-off

scores for the four classes with equal probability to each quartile/class. For Method 2, denote as $5\sum_{i=1}^{5} p_{i5} - \sum_{i=1}^{5} p_{i1}$ as $D_{Y(Max)-Y(Min)}$ and divide $D_{Y(Max)-Y(Min)}$ into four or five equal parts and generate boundary points for classification of persons in 4 to 5 mutually exclusive classes.

However, classifications using *P*-scores need to be validated with clinical observations. Efficiency of classification by equivalent boundary points (cut-off scores), need to be measured by ratio of similarity within classes and dissimilarity between classes.

Limitations

P-scores in Method 1 and Y_{5L} values in Method 2 depend on the sample. The methods work best for sample of patients suffering from same disease, where homogeneity of treatment and related factors during the follow-up periods can be assumed.

Discussion

Two methods are described to transform raw item-scores to follow Normal distribution with the same score range and satisfy desired properties of measurement including meaningful arithmetic aggregations, minimizing tied scores. Domain scores and test scores follow normal and facilitate better ranking, comparisons and parametric statistical analysis, computation of reliability, validity, etc.

Each method provides total score reflecting total disorder, which can help to find overall index of disability in MS. Method 2 indicates domain-wise status of a patient and helps practitioners to decide priorities and course of action accordingly. However, Method 2 requires significant modifications of existing tests to fit 5D-5L set up.

The proposed equivalent scores are interchangeable with near perfect correlation and are preferred over conversion tables generated from the Crosswalk Studies which may vary by several points and may not provide inverse function for each score.

Conclusions

Considering the theoretical advantages including meaningfulness of operations, better comparison, easy comprehension, Method 1 is recommended with the suggestion to report test score and also domain scores. The later can be used fruitfully for treatment of individual patient. Practioners and researchers can take advantages of the normally distributed *P*-scores with desired properties, including quantification of changes by longitudinal data and better evaluation of psychometric parameters. Future studies with multi-data set involving longitudinal data may be undertaken for generalization of findings along with psychometric properties of the proposed transformations.

Declaration

- **Ethical statement:** The methodological paper involved no collection of data from men and animals.
- **Acknowledgments:** Nil
- **Conflicting of Interest:** No potential conflicts of interest concerning the research, authorship, and/or publication of this article.
- **Funding:** The author received no financial support for the research and/or authorship of this study.
- **Authors' Contributions:** Sole author: Conceptualization; Methodology; Analysis; Writing and editing the paper.

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