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Case Report

Association between Multiple Sclerosis and Cardiovascular Dysfunction

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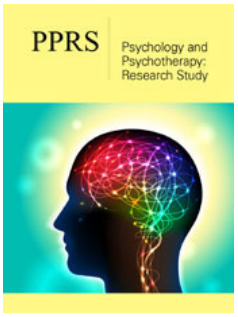
ISSN: 2639-0612



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Submission: April 12, 2023
Published: April 28, 2023

Volume 6 - Issue 5

How to cite this article: Satyendra Nath Chakrabartty. Association between Multiple Sclerosis and Cardiovascular Dysfunction. Psychol Psychother Res Stud. 6(5). PPRS. 000648. 2023.
DOI: 10.31031/PPRS.2023.06.000648

Abstract

Background: Empirical studies indicate association of Multiple Sclerosis (MS) with increased risks of Cardiovascular Diseases (CVDs). However, controversial results emerged.

Objectives: To measure the association between MS and CVD using pathological data and scales to assess s MS and CVD.

Methods: The paper provides an assumption-free method to convert item scores to normally distributed scale scores, avoiding limitations of scales to assess MS or CVD satisfying desired properties. Binary and categorical pathological data may also be transformed to follow normal and data in ratio scale may be standardized followed by transformation and added with scale scores.

Result: Association through contingency table need meaningful scale scores to obtain the cell frequencies. Proposed scores can classify the sample in relevant classes through equivalent scores and find cell frequencies. Associations by correlations are preferred over frequency based measures. However, correlations may not imply linearity.

Conclusion: Normally distributed proposed scores ensure meaningful addition of item scores to get dimension/scale scores for individuals and contribute to improve scoring of instruments. Such scores facilitate better comparisons, measurement of association, statistical tests and identification of areas requiring changes in clinical practice, treatment protocols, community program management and estimating population parameters and testing of statistical hypothesis.

Keywords: Multiple sclerosis; Cardiovascular disease; Contingency table; Normal distribution; Transformations

Introduction

Multiple Sclerosis (MS) is a chronic neurological disorder, associated with inflammation and demyelination of the central nervous system with frequent relapsing-remitting episodes and axonal degeneration leading to irreversible progressive invalidity. MS may affect cardiovascular functions in different ways leading to problems of heart rhythm and rate, left ventricular systolic function, pulmonary edema or cardiomyopathy, etc. and also by brainstem lesions affecting autonomic pathways in the medulla, overall plaque burden and thus increases risk of Cardiovascular Disease (CVD) [1]. Considering Composite Autonomic Scoring Scale (CASS) and Heart Rate Variability (HRV) [2] found significantly higher burden of autonomic dysfunction among patients with Primary Progressive MS (pwPMS) than patients with relapsing-remitting MS (pwRRMS), which was particularly evident for sweating dysfunction. The occurrence of CVD were observed among patients with MS and existence of association between them [3,4]. Genetic liability to MS was found to be associated with increased risks of Coronary Artery Disease (CAD), Myocardial Infarction (MI), Heart Failure (HF), stroke, but not with Atrial fibrillation or other stroke subtypes (Large Artery Stroke (LAS), Cardioembolic Stroke (CES), and Small Vessel Stroke (SVS) [5]. Controversial results emerged on risk of occurrence of CVD and death among MS patients [6]. However, the cause and effect relationship between MS and CVD are not exactly known [7].

Association between MS and CVD can be approached using biomarkers, genetical configurations or by scales to assess MS and CVD. Instruments to measure functional deficits of MS patients with Coronary Heart Disease (CHD) consider items which differ in item formats, dimensions, scoring systems, etc. and are not comparable. Scores of such scales suffer from methodological shortcomings. The paper describes limitations of scales measuring MS and CVD and provides assumption-free method to convert ordinal item scores to proposed scores following normal distribution, satisfying desired properties for better comparisons, measurement of association, facilitating identification of areas requiring changes in clinical practice, treatment protocols, community program management and estimating population parameters and testing of statistical hypothesis.

Literature survey

Autonomic Symptom Profile (ASP) with 169 items in 11 dimensions of autonomic function provides clinically relevant scores of autonomic symptom severity and distribution of symptoms. The scale was validated with the Composite Autonomic Symptom Score (COMPASS) containing 72 items distributed in 11 dimensions and an additional 12 items to generate two validity scores [8]. Major limitations are:

A. The highly complicated scoring system of COMPASS involves computer analysis to generate scores which may be inconsistent.

B. ASP is time consuming even if it is shortened to items relevant for COMPASS.

C. Some COMPASS items are less meaningful or redundant for scoring severity of autonomic functions and symptoms.

D. Significant overlapping of COMPASS dimensions like syncope with orthostatic.

E. The relevance of reflex syncope for assessment of autonomic deficits is not beyond questions.

The instrument was redesigned to a simplified version [8] known as COMPASS 31 containing binary items for presence (1) or absence of the symptom (0); 4-point items for time course of a symptom (0 to 3); 3-point items for frequency of symptoms (0 to 2), severity of symptoms (1 to 3), changes in bodily functions (0 to 2). COMPASS 31 has been used to evaluate autonomic dysfunction in people with systemic sclerosis [9] and other diseases like Parkinsonism, Fibromyalgia (FM) and small-fiber polyneuropathy. Popular HRV analysis to detect Cardiovascular Autonomic Neuropathy (CAN) through electrocardiography recordings [10] was preferred over traditional CARTs since HRV is more sensitive and accurate [11]. A too simplistic framework to link HRV frequency components (LF and HF) with the sympathetic and parasympathetic autonomic nervous system is the major limitation of HRV [12]. Positive correlation was found between the questionnaire measuring FM severity (FIQ) and COMPASS [13] implying that autonomic dysfunction is inherent to FM. Cohort study by [14] covering people with MS and without MS (matched control) found that MS is associated with an increased risk of CVDs, which cannot be explained by traditional vascular risk factors.

Other MS scales (Illustrative)

20-point Expanded Disability Status Scale (EDSS) with binary, 5-point and 6-point items measures disability, functions of CNS and progression of MS, where score ranges from zero (indicating "Normal") to 10 (death by MS) with 0.5 point steps combining eight Functional System (FS) [15]. EDSS with two modes (bimodal) has been criticized for its limitations [16]. Based on changes in assessment [17], proposed calculation of brain functions FS in EDSS by $EDSS_{Basal}$ and $EDSS_{Modified}$ using the scores from the Brief International Cognitive Assessment for MS (BICAMS) [18]. But $EDSS_{Basal}$ and $EDSS_{Modified}$ follow different distributions and comparison of means by t-statistics, assuming normally distributed scores is unjustified.

Guy's Neurological Disability Scale (GNDS) with 12 functional dimensions is obtained by adding dimension scores, each ranging between 0 to 5 assuming equal importance to the dimensions. Here, a higher score implies more disability [19]. Suggestions of Neuro status by modifying gait assessment criteria and including new definitions of each FS by [20] does not propose a single test or homogeneous assessment criteria. A single clinical outcome measure of sustained disease progression, failing which an integration of outcome measures reflecting various stages of MS, was preferred [21].

CVD-specific instruments

Seattle Angina Questionnaire (SAQ): Aims at measuring FS of CAD patients. SAQ with 19 items on five clinically relevant dimensions: physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception/quality of life is often used as a HRQoL instrument because seven of its 19 items relate to emotional health. However, SAQ does not provide a single summary score of a patient reflecting overall assessment of patients' health status. A shortened version SAQ-7 with 7 number of 6-point items was derived with provision of single summary score [22]. Diary reports were preferred over SAQ [23].

Minnesota Living with Heart Failure (MLHF) questionnaire: Contains 21 items; each in 6-point scale (0 to 5) where $0 \leq$Total score≤ 105. It provides scores for two dimensions, physical and emotional, and a total score (assuming one-dimensionality). Researchers differed in the factor structure of MLHF. The existence of the third factor was confirmed [24].

Myocardial Infarction Dimensional Assessment Scale (MIDAS): The 35 items of MIDAS questionnaire are arranged in hierarchy order to assess seven dimensions, is designed specifically for patients with angina, MI or heart failure [25]. Each dimension is scored separately using Mokken Scaling Procedure, a computer program on the basis of a range of diagnostic criteria.

Cardiovascular Limitations and Symptoms Profile (CALP): Involves 37 items, four symptoms subscales and five functional limitation subscales [26]. Each subscale contains four to six items and scores are weighted to provide a total for each subscale.

Observations

Major disadvantages of summative scale scores are:

A. Addition of item scores and dimension scores are not meaningful due to non-satisfaction of equidistant property, assigning equal importance to the items/dimensions despite different contributions of items/dimensions to total score, different correlations between item/dimension and total score, different factor loadings, etc.

B. Unknown and different distributions of item scores creates problems in interpreting and finding distribution of X±Y and further use of X±Y

C. Avoid zero scores. Score 0-1 items as say 1-2.

D. Fails to generate normally distributed scale scores, which is the basic assumption of analysis like t-test, Analysis of Variance (AVOVA), Principal Component Analysis (PCA), Factor Analysis (FA), estimation and testing of population parameters, etc.

Remedial actions on shortcomings of various scales on MS and CVD

a) Follow the convention higher score ⇔ better health status to ensure same score direction. This may require inverse scoring of items that do not follow the convention.

b) Transform positive ordinal item scores to continuous, monotonic scores following Normal distribution in a fixed score range (say 1 to 100). Find dimension scores and scale scores as sum of the normally distributed item scores so that distributions of dimension/scale scores are also normal.

c) Normally distributed scale scores satisfy desired properties to undertake parametric analysis and also help to improve Receiver Operating Characteristic (ROC) curve and Area Under The Curve (AUC) analysis [27].

Measures of association

Frequency based approach: Choose a suitable test of MS and another test for CVD where outcomes of each test is dichotomous, either positive or negative or high and low severity. Association between two outcome variables may be arrived using 2×2 contingency table as follows (Table 1): Associations considering cell frequencies of contingency table are:

a. Chi-square measure of association $\chi^2 = \sum \frac{(f_{observed} - f_{expected})^2}{f_{observed}} \sim \chi^2$ distribution with (r-1)(s-1) degrees of freedom for r-rows and s-columns of r×s contingency table. Here, $f_{expected}$ for the (i–j)-th cell is $\frac{Total\ of\ i-th\ row \times total\ of\ i-th\ colomn}{Grand\ total}$. H_0 *for* χ^2 test is that the two diseases are independent; that is, the level of MS does not predict the level of CVD.

b. Pearson's Contingency Coefficient(C) is a measure of the relative (strength) of association between two variables and given by $C = \sqrt{\frac{x^2}{N + x^2}}$ where N is the sample size. C can be used for incidence and also prevalence studies but may not be applicable for paired data.

c. Cramer's V-Coefficient: x^2 may get increased for large N, even if the variables may not have any substantive relationship. Cramer's V-Coefficient helps to improve association by $V = \sqrt{\frac{x^2}{N^{(q-1)}}}$ where q = minimum (r, c) and 0≤V≤1

Table 1: Contingency table-clinical evidences and tests.

		Clinical and Pathological Evidences Showing Existence/Absence of CVD		Total
		Yes	No	
MS test	Positive	True Positive (TP) $f_{(T+D+)}$ (A)	False Positive (FP) $f_{(T+D-)}$ (B)	Row total (R_1) (A+B)
	Negative	False Negative (FN) $f_{(T-D+)}$ (C)	True Negative (TN) $f_{(T-D-)}$ (D)	Row total (R_2) (C+D)
Total		Column total (C_1) (A+C)	Column total (C_2) (B+D)	Grand Total (N) (A+B+C+D)

Other indices are:

Odd Ratio (OR) = $\frac{f_{(T+D+)} \times f_{(T-D-)}}{f_{(T+D-)} \times f_{(T-D+)}} = \frac{AD}{BC}$

Relative Risk (RR) = $\frac{f_{(T+D+)}}{R_1} / \frac{f_{(T-D-)}}{R_2} = \frac{A}{A+B} / \frac{C}{C+D}$

RR is usually calculated for cohort studies where patients with and without exposure (say MS) are followed for particular outcome (say CVD). RR=1⟹ incidence is the same among those exposed and unexposed. OR is calculated for case-control or cross-sectional studies and is interpreted in line with RR. OR=1⟹ no association exists. OR<⟹ exposure is protective i.e. exposure is less likely among the case group, and OR> 1⟹ exposure is a risk factor i.e. exposure is less likely among the control group. Both RR and IR fail if the assumption of independence is violated. Confidence intervals of both OR and RR can be formed to reflect range of uncertainty.

Measures of association based on contingency table need to find meaningful scale scores to obtain frequency of True positive, false positive, false negative and true negative. One solution is through equivalent score combinations $\{X_0, Y_0\}$ defined as

$$\int_{-\alpha}^{X_0} f(X)dx = \int_{-\alpha}^{Y_0} g(Y)dy \qquad (1)$$

where the score X_0 in a scale (MS) with density function f(X) is equivalent to the score Y_0 in another scale (say CVD) with density function g(Y) i.e. area under f(X) up to X_0=area under g(Y) up to Y_0. Normally distributed scores of MS and CVD help to solve (1) and

find equivalent scores Y_0 of CVD for a given score X_0 of MS or vice versa by solving (1) using standard Normal table [28]. If X_0 is the cut-off score for MS (people with scores $\geq X_0$ are suffering from MS and people with score < X_0 are MS-negative), with equivalent score Y_0 of CVD, then

True positive = number of people with scores $X_i \geq X_0$ *and* $Y_i \geq Y_0$.

False positive is the number of people with $X_i \geq X_0$ *and* $Y <_i Y_0$.

False negative = number of people with scores $X_i < X_0$ *and* $Y_i \geq Y_0$.

True negative= number of people with scores $X_i < X_0$ *and* $Y_i < Y_0$.

Such classification of the sample avoids subjectivity in deciding cell frequencies of 2×2 contingency table. A cut-off score X_0 may be decided by ROC curve. ROC curve was generated for each validated miRNA, and AUC for MS versus Healthy Control group [29]. However, parametric method may result in improper ROC curve if data violate the assumptions of normality and similar within-group variances.

Other measures of association

Spearman ρ based on ranks of individuals in two tests fails when data show grouped frequency distributions. Accuracy of Spearman ρ is much less than correlation coefficient between scores of two scales (r_{XY}) measuring two diseases. Measures based on correlation are preferred over frequency based measures and Spearman ρ. However, high correlation may not imply linearity between two variables. For example, if X takes integer values from 1 to 30, $r_{x,x}^2$ = 0.97. Thus, linear regression Y=α+βX needs to test normality of error scores and test H_0:S^2_E=0 to ensure linearity. In addition, homogeneity of data on X or Y or both can lower value of r_{XY}. Violation of assumptions of correlation may lead to biased, inconsistent and invalid estimates [30]. Effect sizes, which indicate the magnitude of the difference between groups (by t-test), measures of variability (by F-test), etc. are more informative when interpreting epidemiologic data [31]. Such tests assume normally distributed data.

Converting ordinal data to follow Normal distribution

Let X_{ij}>0 be the response of an individual in the j-th response category of the i-th item. For a 5-point item, Revised Score (RS) will be $W_{ij}X_{ij}$ where W_{ij}'s are positive weights to different levels of the item satisfying $\sum_{j=1}^{5} W_{ij} = 1$. RS will be equidistant and monotonic if $W_1, 2W_2, 3W_3, 4W_4$ *and* $5W_5$ forms an arithmetic progression where common difference α>0. For each item, find maximum (f_{max}) and minimum frequency (f_{min}) of the levels. Find initial weights $\omega_{ij} = \frac{f_{ij}}{n}$. Arrange the ω_{ij} so that $\omega_{i1} < \omega_{i2} < \omega_{i3} < \omega_{i4} < \omega_{i5}$ where $\omega_{i1} = \frac{f_{\min}}{n}$ and $\omega_{i5} = \frac{f_{\max}}{n}$. Let intermediate weight $W_{i1} = \omega_{i1}$ Find the common difference α so that $W_{i1} + 4\alpha = 5W_{i5} \Rightarrow \alpha = \frac{5f_{\max} - 5f_{\min}}{4n}$.

Define other intermediate weights as

$$W_{i2} = \frac{\omega_{i1} + \alpha}{2}, W_{i3} = \frac{\omega_{i1} + 2\alpha}{3}, W_{i4} = \frac{\omega_{i1} + 3\alpha}{4} \text{ and } W_{i5} = \frac{\omega_{i1} + 4\alpha}{5}$$

Get final weights $W_{ij(final)} = \frac{W_{ij}}{\sum_{j=1}^{5} W_j}$ enabling $W_{ij(final)} = 1$ and $j.W_{j(final)} - (j-1).W_{(j-1)(final)} = cons\tan t$, value of which will be different for different items.

Observations

A. $W_{j(Final)}$ are based on empirical probabilities.

B. If f_{ij}=0 for a particular j-th level of an item, this can be taken as zero value for scoring k-point items as weighted sum.

C. Equidistant scores (E) as weighted sum are continuous implying better admissibility of arithmetic aggregation. E-scores or linear transformations of E-scores facilitate addition with bio-markers (usually in ratio or interval scales)

Standardize E-scores by $Z_{ij} = \frac{E_{ij} - \overline{E_i}}{SD(E_i)} \sim N(0,1)$. Convert the Z-scores to proposed P-scores by

$$P = (100-1) * \left[\frac{Z_{ij} - M\,\text{in}(Z_{ij})}{M\,\text{ax}(Z_{ij}) - M\,\text{in}(Z_{ij})} \right] + 1 \qquad (2)$$

For the i-th item, $P_i \sim N(\mu_i, \sigma_i^2)$ and $1 \leq P_i \leq 100$.μ_i and σ_i^2 can be estimated from the data. P-score of an item can be obtained irrespective of number of items and number of response-categories in items. Pathological data could be binary or categorical or in ratio scales. Binary and categorical data may be transformed to follow normal by the above said method and ratio scale data may be standardized followed by transformation (2) and added. The dimension score of an individual is sum of P-scores of relevant items. Scale score is similarly taken as sum of domain scores or P-scores of all items.

Properties

Dimension scores (D_i) and scale scores (S_i) of the i-th individual are continuous, monotonic, normally distributed with better admissibility of arithmetic aggregation. They facilitate parametric analysis including estimation of population mean (μ), population variance (σ^2), confidence interval of μ, testing hypothesis like H_0: $\mu_1 = \mu_2$ or H_0: $\sigma_1^2 = \sigma^2_2$ etc. either for longitudinal data or snap-shot data. Same range of item-wise P-scores avoids variation due to different score-ranges. However, variance of dimension scores may vary depending on the number of items in dimensions. The dimensions can be ranked based on elasticity, defined by $\frac{\%change\ in\ scale\ scores}{\%change\ in\ j-th\ domain}$. Percentage progress/deterioration of the i-th person during successive time-periods is given by $\frac{S_{i(t)} - S_{i(t-1)}}{S_{i(t-1)}} \times 100$, reflecting responsiveness of the scale and also effectiveness of a treatment plan. $S_{i(t)} - S_{i(t-1)} > 0$ implies progress in t-th period over (t-1)-th period. The reverse is true for $S_{i(t)} < S_{i(t-1)}$. Deterioration in terms of scale scores may be probed to identify dimension(s) showing deterioration for possible corrective actions or treatment plan/care.

Progress for a group of persons is reflected if $\overline{S_{(t)}} > \overline{S_{(t-1)}}$. Normality of S_i helps to test H_0: $\mu S_t = \mu S_{(t-1)}$. Significance of responsiveness of a

scale in terms of $\frac{S_{i(t)} - S_{i(t-1)}}{S_{i(t-1)}}$ can be tested since ratio of two normally distributed variables follows χ^2 distribution.

Testing of significance of progress i.e. testing H_0: $Progress_{(t+1)over\ t}=0$ may avoid need to find minimal important difference of a scale for comparing changes over time among the group of patients. Plotting of progress of a patient or a group of patients across time can be used to compare progress pattern i.e. response to treatments from the start.

Discussion

Limitations of scales to assess MS or CVD may be avoided by the proposed transformations. Binary and categorical pathological data may be transformed to follow normal by such transformations. Ratio scale data may be standardized followed by transformation (2). Such transformed data facilitate meaningful addition. Dimension score (D_X) is sum of P-scores of relevant items following normal where parameters are derived from the data. Scale score (S_X) is similarly taken as sum of domain scores or P-scores of all items.

Measures of association based on contingency table need to find meaningful scale scores to obtain frequency of True positive, False positive, False negative and True negative. Proposed S_X following Normal distribution help in meaningful aggregation of item scores and help in classification of the sample avoiding subjectivity in deciding cell frequencies of 2×2. Contingency table, where cut-off score for diagnosis may be decided by ROC curve. In addition, proposed scores facilitate parametric analysis including estimation of population parameters like mean (μ), variance (σ^2), confidence interval of μ, testing hypothesis like H_0: $\mu_1=\mu_2$ or H_0: $\sigma_1^2=\sigma_2^2$ etc. either for longitudinal data or snap-shot data, ranking of dimensions based on elasticity, etc. Association between MS and CVD in terms of correlations is preferred over frequency based measures. However, correlations may not imply linearity.

Conclusion

The proposed method generating normally distributed scores contributes to improve scoring of instruments. It is suggested to convert ordinal item scores to normally distributed scores which help in better comparisons, ranking, assessing associations among scales. Future empirical investigations are proposed with multi data sets to find associations including ROC–AUC analysis with normally distributed data.

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