Short Communication

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.58.009186

Interpretation of Fatigue as an Independent Generic Patient Reported Outcome in Patients with Rheumatoid Arthritis

László Hodinka[1]*, Barbara Hodinka[2], Vivien Ifju[1] and Edit Vereckei[1]

[1]*National Musculoskeletal Institute, National Institute of Rheumatology and Physiotherapy, Hungary*

[2]*Västernorrland Psychiatric Clinics, Sweden*

***Corresponding author:** László Hodinka, National Musculoskeletal Institute, National Institute of Rheumatology and Physiotherapy, H-1023 Frankel Leo Str 25-29, Budapest, Hungary

ARTICLE INFO

Received: September 03, 2024

Published: September 16,2024

Citation: László Hodinka, Barbara Hodinka, Vivien Ifju and Edit Vereckei. Interpretation of Fatigue as an Independent Generic Patient Reported Outcome in Patients with Rheumatoid Arthritis. Biomed J Sci & Tech Res 58(4)-2024. BJSTR. MS.ID.009186.

ABSTRACT

The hypothesis of our research is that the perception of rheumatoid arthritis patients about their disease may be influenced by their personality traits. In our previous studies, we constructed individual profiles and clusters based on rheumatoid arthritis patients' responses to self-assessment questionnaires. In this study we looked for personality assessment tools that could be used to verify the hypothesis. Patients with rheumatoid arthritis (95 women and 10 men) were studied. A composite index and hierarchical cluster were constructed based on the responses of 105 with rheumatoid arthritis to disease-specific and generic questionnaires. The personality tests used were the Temperament and Character Questionnaire, the Big Five Five-Factor Personality Model and the Patient Health Questionnaire in a subgroup of forty participants. The Fatigue subscale of the FACIT Functional Assessment of Chronic Illness Therapy questionnaire correlated well with clinical scales. The majority of respondents rate their condition unanimously as severe or mild in all tools. However, about one third of patients gave conflicting assessments of their physical and mental/emotional condition. When comparing the Temperament/Character and Five Factor models the former was found more reliable in finding associations. Patient Health Questionnaire showed minimal risk of depression. Fatigue sub-dimensions constructed for the current study accordingly reflect the clinical self-assessment of patients with rheumatoid arthritis and confirm our findings on the applicability of personality tests. The FACIT Fatigue subscale may be useful as an independent generic self-assessment tool for analysing other chronic musculoskeletal conditions.

Keywords: Rheumatoid Arthritis; Severity Profile; Clusters; Fatigue; Personality Traits

Abbreviations: B-IPQ: Brief Illness Perception Questionnaire; CFS/ME: Chronic Fatigue Syndrome/Myalgic Encephalitis; DAS 28: Disease Activity Index 28 Joints; FACIT: Functional Assessment of Chronic Illness Therapy; PhGA: Physician Global Assessment; PHQ-9; Patient Health Questionnaire; PRO: Patient Reported Outcome; PtGA: Patient Global Assessment; RADAI-5: Rheumatoid Arthritis Disease Activity Index 5 Items; RAID: Rheumatoid Arthritis Impact of Disease; RRB Index: Mean of RADAI-5, RAID and B-IPQ Questionnaire Scores; SDAI: Simplified Disease Activity Index; TCI: Temperament and Character Inventory; TJC: Tender Joint Count; VLA: Valued Life Activities Questionnaire

Introduction

The underlying hypothesis of our multi-phase research is that patients with rheumatoid arthritis (RA) in their self-assessment (Patient Reported Outcomes, PROs) is influenced by their personality traits. Our results so far have demonstrated that a subset of patients rate the physical and functional impact and mental/emotional challenges of the disease differently from objective biomarkers and composite activity indices used in clinical practice. These indicators have been summarized in patient profiles and classified into hierarchical clusters [1]. We have previously observed that the personality profile of patients with rheumatoid arthritis is similar to that of patients with fibromyalgia [2]. This has been confirmed by several studies, with fibromyalgia generally considered a pain-processing disorder observed frequently with depressive and anxiety reactions as part of the pathology of rheumatoid arthritis or as comorbidities [3,4]. Therefore, in the present study, we investigated how patient profiles constructed by PRO instruments only are related to personality profiles detected by personality tests. To verify the hypothesis, we intend to use the selected instrument in the following phases of the research. In order to validate the self-assessment questionnaires for RA patients, a sub-study we compared the domains of the questionnaires with the domains of the generic FACIT instrument (Functional Assessment of Chronic Illness Therapy).

Earlier and also in the current study we found that, in addition to the strong correlations of the FACIT subscales, the Fatigue subscale had a particularly strong association with the PRO instruments tested. This subscale is currently used as a stand-alone PRO questionnaire (FACIT Fatigue Scale Version 4) in a number of studies investigating the effects of chronic disease. Therefore, now we analysed the facets of the FACIT Fatigue subscale questionnaire from the perspective of how well their subscale items reflect the personality test domains. Fatigue is a multifaceted phenomenon as a continuum from the physiological load dependent tiredness to pathological, chronic, centrally processed psychologically driven misleaded effort to adapt [5,6]. This latter is in close association with age and disease-related frailty, chronic pain intensity and interference domains [7] and is regarded as an entity of chronic fatigue/myalgic encephatlitis (CF/ME) [8]. In our approach and phrasing fatigue is the individually experienced phenomenon and its functional and mental interference and fatigability is the lack of resilience to the fatigating risk factors. Published fatigue biomarkers are usually biomarkers of the underlying disease [9,10], but the state and severity of fatigue are judged using self-assessment tools [11]. Fatigue is rather a condition in a given life situation like pain and not a well-defined outcome. The aim of this study is to help to select a personality test that may be suitable for exploring the instinctive background of self-evaluation in patients with rheumatoid arthritis.

Materials and Methods

Patients

We included 105 patients with rheumatoid arthritis registered in our database. Demographic data: 95 females, 10 males, mean age 60,4 years, mean duration of disease 18,9 years. A representative subgroup of 40 patients was formed from the whole group. The median of their DAS 28 indices was 2.6 DAS 28 scores which is according to the DAS 28 grading the remission cut-off. The means of the subgroup indicators did not differ significantly from the corresponding means of the whole cohort.

Instruments and Indicators

Fr all patients, we recorded the components of the DAS 28 and SDAI disease activity indices [12] and the degree of pain as reported by patients on a 100 mm visual analogue scale. Patients in the entire group completed the Rheumatoid Arthritis Disease Activity Index 5, RADAI-5, Rheumatoid Arthritis Impact of Disease, RAID, Brief Illness Perception Questionnaire, B-IPQ and Valued Life Activities, VLAQ questionnaires [1]. Subgroup members also provided responses to the full FACIT questionnaire [13], two personality assessment tools (Temperament and Character Inventory, TCI) [14] and the Five-Factor Big Five questionnaire [15]and the depression risk questionnaire (Patient Health Questionnaire, PHQ-9) [16]. The thirteen questions of the Fatigue subscale of the FACIT questionnaire were grouped into three sub-dimensions (vitality: items 1,2, 4,7; functionality: items 5, 8, 9,10, 11; and mental challenges: items 3, 6,12,13) according to the item targets. The content of the Fatigue subscale and that of the sub-domains developed were also compared against other subjective indicators that could be associated with the fatigue phenomenon. These are the VAS score for pain, the Patient Global Assessment (PtGA VAS) and the Physician Global Assessment (PhGA VAS) quotient and the Tender Joint Count (TJC) [17]. The questionnaires and their dimensions used in the study are presented in Table 1. The validated and licensed Hungarian versions of the questionnaires were used.

Table 1: Questionnaires used.

Rheumatoid Arthritis Disease Acitity Index 5. Joint pain and swelling the past half year, - in the past week, current pain and health, morning joint stiffness and duration. Five items, 10 point Likert scale, mqxumum score 50.
Rheumatoid Arthritis Impact of Disease. Pain, activities, fatigue, sleep, physical well-being, emotional state, coping. Seven items, 10 point Likert scale, maximum score 70.
Brief IPQ Illness Perception Questionnaire. Impact of the disease, expected duration, control of the disease, confidence in treatment, perceived symptoms, anxiety, knowledge of the disease, emotional attitude. Eight items, 10 point Likert scale, maximum score 80.
Valued Life Activities questionnaire. 14 activities daily living, social and leisure activities
FACIT Functional Assessment of Chronic Illness Therapy. Physical, social/family, emotional and functional well-being, fatigue. Five domains, 6 to 13 items each, Five point Likert cales, maximum score 160, Fatigue subscale maximum 13.
TCI Temperament and Character Inventory. Temperament dimensions: novelty seeking, harmavoidance, reward dependence, persistence. Character dimensions: self-dicetedness, cooperativeness, self-transcendence. Different item versions, the Hungarian 55 item version was used. True/false answers or five point Likert scores. Classification according to the majority of scores.
Five Factor personality model „Big Five Inventory". Antagonistic self-characterizing statements in five dimensions: extraversion, agreeableness, constientiuousness, neurocitism and openness. We used the 44 item version, five point Liker scales. Classification ccording to the majority of scores.
Patient Health Questionnaire, PHQ-9. Nine questions on depression, fatigue, sleep disturbance, loss of motivation, concentration, slowing down, anxiety, worry, and self-aggression. Three point Likert scale for each. Maximum score 27. Evaluation: five score intervals grading of severity (severe risk: 20-27).

Statistical Analysis

Descriptive statistics were used to record the score values and derived data for the indicators. On the basis of interquartile range cut-points, patients were classified according to severity. The content of the questionnaires was verified by comparing them with the domains of the FACIT questionnaire. Correlations were used to find the best clustering indicators. the RADAI-5, RAID and B-IPQ questionnaires. On this basis the median values of the three pure PRO questionnaires, the RADAI-5, RAID and B-IPQ questionnaires were considered as the levels of hierarchical clustering. The averaged scores (RRB index) of the three selected clustering questionnaires represent patients' multifaceted self-assessment of the severity of their disease. Using the three PRO questionnaires, eight clusters were again formed according to the hierarchical algorithm described previously (1 BJSTR). Hypothesis-testing and descriptive statistical evaluation were performed using Microsoft Excel 365 programs (mean, standard deviation, 95% confidence limits, quartiles and extremes, Spearman correlation and simple linear regression) for continuous variables and Social Science Statistics programs (chi-square test and significance tables) for categorical variables. Probability limits of statistical significance were set and marked as p-value thresholds of 0.05, 0.01 and 0.001. The case numbers (105 and 40) provide adequate statistical power.

Ethic Approval

The research was conducted ed in accordance with the Medical Association's Declaration of Helsinki and the protocol was approved by the institutional, regional and Health Sciences Council ethical boards (licensed under 191/2013 and BM/12470-3/2024).

Observations

Clinical Profile and Cluster

Currently, the clinical patient profile and the hierarchical cluster dendrogram were constructed according to the previously described algorithm (1) using the three pure PRO instruments (RAID-5, RAID and B-IPQ) (Figure 1). It was found that, as such, sixty-seven percent of the 105 respondents who answered in unison could be classified as either "high" (36) or "low" (31) on all three indicators (i.e., moderate or severe). The intermediate "mixed" severity sets include patients who have a predominantly low or high level of some aspect of their self-assessment as expressed in their PROs (i.e. their PRO profile). The clusters of patients with lower inflammatory and functional PRO scores in addition to those with significant mental distress the (third, fifth and seventh clusters represent 21% of those studied) are the most notable (case numbers in the Figure 1. are rounded percentages to the nearest integers).

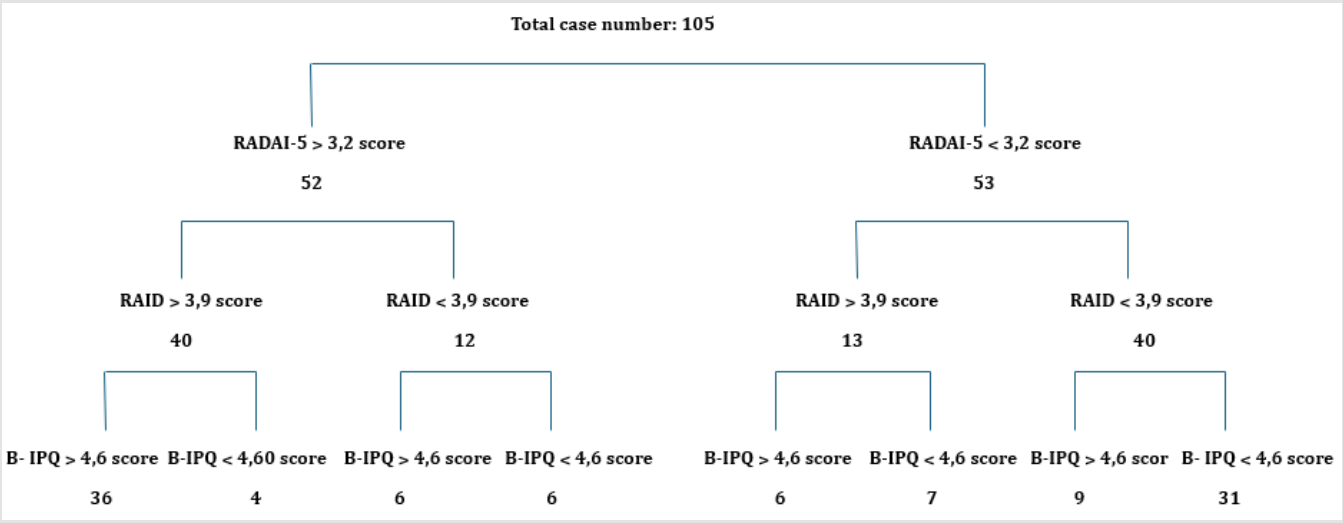

Figure 1: Clusters at clustering levels and case numbers. Cutoffs are the medians of the respective questionnaire scores.

Correlations Between the Scores of the Responses to the Questionnaires

The regression of the summed response scores of the three cluster questionnaires and the total Fatigue subscale scores is illustrated in Figure 2. The regression diagram proves (R^2 = 0.4, beta 0,8, p<0,001) that the points fit the regression line well and fall within the confidence interval and the prediction interval. This allows for the assumption that the correlations between the Fatigue subscale sub-domains will correctly reflect the associations with the content of the relevant PRO answer scores. The correlations between the clinical indicators (including the indices of the three cluster-forming PRO tools and their average score, the composite RRB index and the Fatigue subscale and the sub-domains are presented in Table 2.

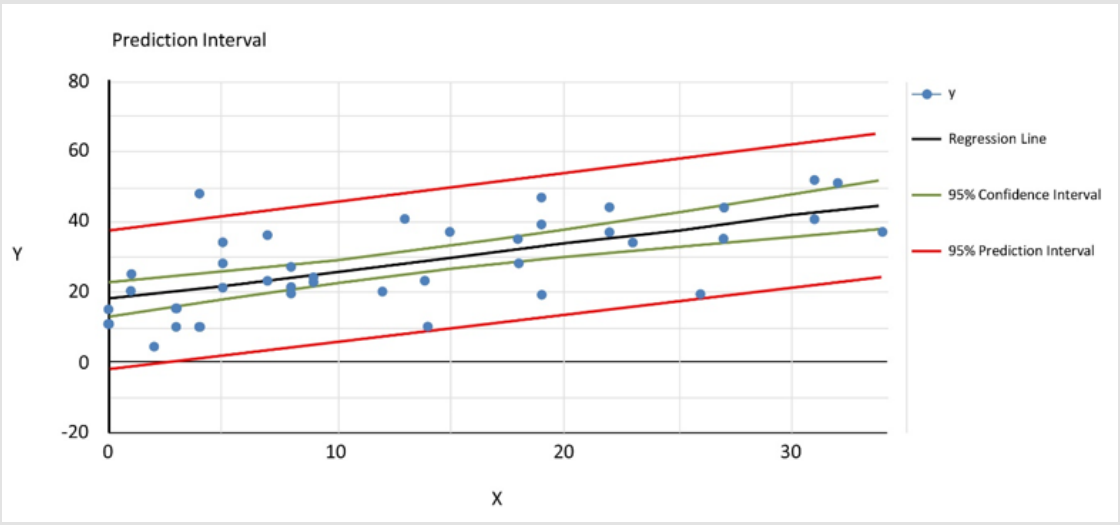

Figure 2: Linear regression of RRB index (RRB: The Rheumatoid Arthritis Disease Activity Index 5, Rheumatoid Arthritis Impact of Disease, Brief Illness Perceprion Questionnaire summed score), Y RRB mean score, X FACIT Fatigue subscale total sore. Regression line equation: $\hat{Y} = 17.5023 + 0.8032X$, X predicted Y, R2 =0 .42, $p < 0.001$. $\beta = 0.8$, $p < 0.001$. R = the correlation coefficient. Explanation in the text.

Table 2: Cross-correlations of Patient Reported Outcome questionnaire and FACIT Fatigue total and Fatigue sub-domain indices.

FACIT total and sub-domension indices PRO questionnaires	FACIT Fatigue total score index Spearman rho and significance	Fatigue sub-domain indices Spearman rho and significance		
		Lack of Vitality	Loss of Activity	Mental Exhaustion
RADAI-5	0,5435 ***	0,5154 ***	0,4843 **	0,5711 ***
RAID	0,6258 ***	0,5961 ***	0,5472 ***	0,6141 ***
B-IPQ	0,5438 ***	0,5619 ***	0,3655 *	0,5689 ***
VLA	0,6712 ***	0,5062 ***	0,7211 ***	0,7000 ***
PAIN	0,5631 ***	0,5089 ***	0,4865 **	0,4996 ***
PtGA / PhGA	0,6342 ***	0,6374 ***	0,5365 ***	0,5850 ***
TJC	0,2160 n. s	0,1974 n. s	0,0426 n. s	0,1897 n. s
RRB	0,6440 ***	0,6424 ***	0,5294 ***	0,6467 ***

The patients' self-assessment questionnaires separately show a strong significant correlation with the FACIT Fatigue subscale response scores. Among the sub-domains of the Fatigue subscale, mental and vitality scores show a similarly strong correlation with the scores of the three profiling questionnaires and as necessary, with their means (RRB index). The lower correlations for the questions related to functionality indicate that respondents attach less weight to the activities formulated in the sub-domain (i.e. they gave lower scores to these questions). In this light, it is noteworthy that the specifically functional VLA questionnaire has a particularly strong relationship with the Fatigue sub-domain of functionality. Among the subjective indicators, the ratings of pain and general health (the PtGA and PhGA ratios measure the difference between the patient's and the treating physician's ratings) are identical. The provoked pain perception (TJC, Tender Joint Count: the number of joints sensitive to standard pressure) is not at all suitable to prove the hypothesized relationship.

Comparative Analysis of the Personality Test Domain and the Facit Subscale and Sub-Domain Contents

The personality test subscales were also analysed against the Fatigue domains (Table 3). In Table 3, only those relations with a correlation coefficient above 0.1000 are included. Even among them, only those above 0.3000 are considered significant. There is a strong positive relationship between the Harm avoidance factor of the Temperament and Character test and the total FACIT Fatigue and its sub-domains. A weak inverse relationship between the Self directedness factor and the full FACIT Fatigue subscale is measured, but this is not reflected at a significant level in any of the sub-domains. This means that self-directed individuals are more fatigue-prone. The same can be said about the correlation between the Extraversion factor of the five-factor Big Five test and the Fatigue subscale, i.e., inward-turning individuals are more fatigued. A very weak inverse relationship between the Big Five Neuroticism factor, the Openness factor and the vitality domain of the Fatigue subscale, vitality and mental sub-domains can be suspected which does not reach the lowest level of significance in the present sample. On the other hand, the relationship between the PHQ-9, a measure of depression risk, and all Fatigue main and subdomains is extremely strong.

Table 3: Correlations of personality questionnaires and FACIT Fatigue total and Fatigue sub-domain indices.

Personality (questionnaire scores)	FACIT Fatigue total subscale index correlations	Fatigue sub-domain indices correlations Spearman rho and significance		
		Lack of Vitality	Loss of Activity	Mental Exhaustion
TCI harm avoidance domain	0,5754 ***	0,5351 ***	0,4571 **	0,5887 ***
TCI self-directedness domain	-0,3005 *	-0,2385 n. s	-0,2135 n. s	-0,2549 n. s
Big Five Extraversion domain	-0,4388 **	-0,4273 **	-0,2815 n. s	-0,4833 **
Big Five Neuroticism domain	0,1499 n. s	0,2021 n. s	0,0480 n. s	0,0668 n. s
Big Five Openness domain	-0,1419 n. s	-0,1637 n. s	0,0619 n. s	-0,1817 n. s
PHQ-9	0,7630 ***	0,7354 ***	0,6031 ***	0,7436 ***

Discussion

Our data from the rheumatoid arthritis profiling and cluster training study are consistent with those reported in studies measuring different aspects of the disease. Among the self-assessment measures of rheumatoid arthritis patients, the RADAI-5, which measures inflammatory activity, the RAID, which measures physical and functional disease impact, and the generic disease perception questionnaire (B-IPQ) can be used to distinguish patients with inconsistent assessments of their condition. The patient responses analysed in recent publications show a dominance of remission and low disease activity as a result of innovative drugs and target-driven therapeutic strategies. At the same time, some groups of patients show a stronger prevalence of perceived negative disease characteristics, including perceived mental challenges. This contradiction is referred to as the PRO paradox. Examples include the different perceptions of the patient and his/her treating physician [18], psychosocial distress reflected in expectations of "unmet needs" [19,20].

For them, mental support rather than increasing the intensity of drug therapy may help to reduce the disadvantages, even the risks and costs. This confirms the importance of using personality studies to explore the role of trait factors determined in the development of a more negative self-image. Personality is a set of thoughts, feelings and behaviours that characterise an individual and shape how he or she adapts to life situations and interacts with the environment. It is essentially psychobiologically determined, instinctive (temperament), but life experiences lead to psychosocial adaptation (trait, character). Diseases do not alter the biologically determined personality, but temperament can affect decision-making, risk-taking, cooperative or negative behaviour [14]. The disproportionate expression of certain personality traits do not usually reach the level of disease, but can make life difficult, create maladaptive disorders and cumulative conflicts. Trait measures primarily reflect socialisation and adaptation [15]. The content of the personality tests is presented in Table 1.

The subjective perception of the fatigue phenomenon was brought to our attention by the fact that patients' self-assessment questionnaires with different content (activity, function, mental/emotional aspects) showed very strong correlations with the corresponding subscales (physical, emotional, functional and fatigue) of the FACIT generic health status instrument. The Fatigue subscale, in turn, was strongly correlated with all clinical PROs alone, i.e. it reflected all their aspects. The number of publications on fatigue is growing exponentially in the new millennium. Their unanimous conclusion is that fatigue is a heterogeneous but individual experience, like pain. It is universal, not so much linked to specific diseases but to multicausal stress. It can be seen as a continuum phenomenon, with one pole being physiological, protective fatigue due to overload or voluntary overuse. In the middle of the spectrum is the age-related fatigue associated with natural or accelerated ageing, mostly associated with age-related involutional diseases such as osteoporosis or sarcopenia and cancers. This is a concept known as frailty syndrome. The other endpoint is a pseudo-adaptive disorder of the central nervous system associated with infection or autoimmune inflammation [21,22].

The postulated mechanism of its development is the instrumentally measurable central sensitization as much as in the case of the central pain [23]. Its key factor may be the pleiomorphic cytokine Interleukin 6, which activates non-neuronal cells of the central nervous system [24]. Fatigue is measured in a similar way to pain, using Likert scales measuring fatigue intensity and the resulting decrease in activity. A very objective meta-analysis evaluated 27 tests. They concluded that they measured extreme prevalences, had mixed subjective and

objective components, did not contain minimal clinically meaningful difference scores, and were therefore poorly suited to measuring the impact of interventions [25]. Another study identified 120 fatigue items in ten percent of 132 selected frailty publications, with highly variable proportions of physical, functional and mental elements [26]. We classified questions from the six most commonly used Fatigue measures (Fatigue diagnostic, assessment, severity, impact) scales (5-29 items) into vitality, functionality and mental categories. They were included in the questionnaires in highly variable proportions, ranging from 0 to 60 percent. In the FACIT Fatigue subscale we used, these categories were balanced and we therefore consider the sub-dimensions we created suitable for correlation studies. We consider the vitality items as a separate sub-domain to have a similar meaning to the mental/emotional category ones, because it describes both the lack of physical energy and the lack of drive needed for everyday adaptation.

The correlations between Fatigue sub-domains and clinical PROs reflect the independent PRO nature of Fatigue. To measure the subjective nature of Fatigue, we chose pain intensity as a clinical indicator, and the ratio of patient to physician health assessment (PtGA to PhGA ratio). Several publications have demonstrated that patients' PtGA self-assessment is virtually identical to their pain perception, that the physician takes also objective factors into account and therefore generally judges the patient's overall condition a better degree or at least to be the same. This is also manifested in the discrepancy between fatigue and pain intensity and objective indicators [27-29]. This discrepancy is indicated by high correlations with mental sub-domain. The ratio of the number of swollen and tender joints [30] has been proposed as an indicator of fatigue. For mathematical reasons we only used tender joint numbers, and our results did not support this expectation. Other studies have shown that joint tenderness does not correlate with imaging pathology [31]. We found few but convincing associations between fatigue--characteristics and personality traits (Hard avoidance and Extraversion). These are consistent with the results of personality studies in psycho--affective and CFS/ME like disorders [32], and with the results of very small numbers of such.

There are case control studies in the literature reporting on personality tests in patients with rheumatoid arthritis. Among the TCI subscales, weak associations have been described between the Harm Avoidance and Reward dependence subscales and some clinical indicators [33], and between the Harm avoidance and Self-directedness subscales and resilience tests 34 Kiss). Others have found a relationship between the Neuroticism domain of the Eysenck Personality Test measuring character dimensions and certain affective deficits (coping, anxiety, depression) [34,35]. Our own observations are consistent with these findings. The usual perception is that depression and anxiety are common in rheumatoid arthritis. A very thorough study, covering all relevant clinical indicators and lifestyle factors, as well as several autoimmune/inflammatory cytokines and other mediators, active or less active rheumatoid arthritis patients with acute flare ups were studied. All relevant data collected thorough the basic anxiety, depression and CFS/ME like questionnaires were recorded and processed using an extensive statistical apparatus.

Activity data separated patient groups, psychological/psychiatric scales correlated with activity, immunological parameters only conclusively separated the control patient group. Based on their data, the authors consider mental phenotypes to be part of the rheumatoid arthritis endophenotype [36]. Several other analyses have shown that there is no direct correlation between disease activity and severe psychological status. An examination of the supplementary data in the literature shows that, the various measures are consistent with our own results in showing lower levels of depressive and anxiety symptoms, and that a significant proportion of the patients studied do not even have these symptoms. Comprehensive studies agree that among the pre- and comorbid affective psychiatric disorders in rheumatoid arthritis, depression and anxiety are primarily associated with higher levels of pain perception and fatigue [37,38]. Remarkably, however, a recent cluster study of clinical features of the whole human genome and major depression and linked comorbidities from 1.2 million patient records from different European regions found only a weak association between mild depression in old age and certain some autoimmune phenotypes, with no underlying genetic link [39].

Limitations of the Study

This research was conducted as a pilot study on a subgroup of rheumatoid arthritis patients to validate our profiling and clustering algorithm with the FACIT health status measure and to select the personality test that correlates best with them. The low number of cases in the subgroup showed sufficient statistical power at the 0.05 or better probability level at the given degree of freedom. We believe that the evidence of the observed strong correlations allows us to draw the expected conclusions.

Conclusion

Accordingly, the FACIT Fatigue subscale and the Fatigue sub-dimensions constructed for the current study reflects the clinical self-assessment of patients with rheumatoid arthritis and confirm our findings on the applicability of personality tests in future research. The FACIT Fatigue subscale may be useful as an independent generic self-assessment tool for analysing the impact of other chronic musculoskeletal conditions.

References

1. Vereckei E, Hodinka L (2023) Profiling algorithm of rheumatoid arthritis patients based on their disease specific Patient Reported Outcomes. Biomed J Sci Tech Res 51(3): 42716-42722.
2. Hodinka B, Vereckei E, Grósz É, Hodinka L (1998) Temperament, character and pain sensitivity in primary fibromyalgia. Reumatologia (Warsaw) 36(Supplement): 183-184.
3. Evers AWM, Kraaiimaat FW, Geenen R, Jacobs JWG, Bijlsma JWJ (2002) Longterm predictors of anxiety and depressed ood in early rheumatoid arthritis: A 3 and 5 year follow up. J Rheumatol 29(11): 2327-2336.

4. Rathbun AM, Reed GW, Harrold RL (2013) The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review. Rheumatology 52(10): 1785-1794.
5. Louati K, Berenbaum F (2015) Fatigue in chronic inflammation - a link to pain pathways. Arthritis Res Ther 17: 254.
6. Karshikoff B, Sundelin T, Lasselin J (2017) Role of inflammation in human fatigue: relevance of multidimensional assessments and potential neuronal mechanisms. Front Immunol 8: 21.
7. Schumacher BT, Kehler DS, Kulminski AM, Qiao YS, Andersen SL, et al. (2024) The association between frailty and perceived physical and mental fatigability: The Long Life Family Study. J Amer Gerriatr Soc 72(1): 219-225.
8. Jason LA, Sunnquist M, Brown A, Newton JL, Strand EB, et al. (2015) Chronic Fatigue Syndrome versus Systemic Exertion Intolerance Disease. Fatigue 3(3): 127-141.
9. Maksoud R, Magawa Ch, Eaton Fitch N, Thapaliya K, Marshall Gradisnik S, et al. (2023) Biomarkers for myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS): a systematic review. BMC Medicine 21: 189.
10. Zielinski MR, Systrom DM, Rose NR (2019) Fatigue, sleep,and autoimmune and related deisorders. Front Immunol 10: 1827.
11. Knoop V, Mathot E, Louter F, Beckwee D, Mikton Ch, et al. (2023) Measurement properties of instruments to measure the fatigue domain of vitality capacity in community-dwelling older people: an umbrella review of systematic reviews and meta-analysis. Age Ageing 52(Suppl 4): iv26-iv43.
12. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, et al. (2003) A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 42(2): 244-257.
13. Webster K, Cella D, Yost K (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcom 1: 79.
14. Cloninger CR, Svrakic DM, Przybeck TR (1993) A psychobiological model of temperament and character. Arch Gen Psychiatry 50(12): 9975-990.
15. Soto ChJ, John O (2009) Ten facet scales for the Big Five Inventory: Convergence with NEO PI-R facets, self-peer agreement, and discriminant validity. J Res Pers 43(1): 84-90.
16. Kroenke K, Spitzer RL, Williams JBW (2001) The PHQ-9 Validity of a brief depression severity measure. J Gen Intern Med 16(9): 606-613.
17. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, et al. (2014) Developing core outcome measurement sets for clinical trials: OMERACT Filter 2.0. J Clin Epidemiol 67(7): 745-753.
18. Karpouzas, GA, Strand V, Ormseth, SR (2018) Latent profile analysis approach to the relationship between patient and physician global assessments of rheumatoid arthritis activity. RMD Open 4(1): e000695.
19. Lindqvist J, Alfredsson L, Klareskog L, Lampa J, Westerlind H (2022) Unmet needs in rheumatoid arthritis: a subgroup of patients with high levels of pain, fatigue, and psychosocial distress 3 years after diagnosis. ACR Open Rheumatology 4(6): 492-502.
20. Mars N, Kerola AM, Kauppi MJ, Pirinen M, Elonheimo O, et al. (2022) Cluster analysis identifies unmet healthcare needs among patients with rheumatoid arthritis. Scand J Rheumatol 51(5): 355-362.
21. Sotzny F, Blanco J, Capelli E, Castro Marrero J, Steiner S, et al. (2018) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome - Evidence for an autoimmune disease. Autoimm Rev17(6): 601-609.
22. Rohrhofer J, Hauser L, Lettenmaier L, Lutz L, Koidl L, et al. (2024) Immunological patient stratification in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. J Clin Med 13(1): 275.
23. Nijs J, George SZ, Clauw DJ, Fernández de las Peñas C, Kosek E, et al. (2021) Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. Lancet Rheumatol 3(5): e383-e392.
24. Erta M, Quintana A, Hidalgo J (2012) Interleukin-6, a major cytokine in the central nervous system. Int J Biol Sci 8(9): 1254-1266.
25. Elera Fitzcarrald C, Rocha J, Burgos PI, Ugarte Gil MF, Petri M, et al. (2020) Measures of fatigue in patients with rheumatic diseases: A critical review. Arthritis Care Res 72(S10): 369-409.
26. Knoop V, Costenoble A, Azzopardi RV, Vermeiren S, Debain A, et al. (2019) The operationalization of fatigue in frailty scales: a systematic review. Ageing Res Rev 53: 100911.
27. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C (2016) Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther18: 251.
28. Holten K, Paulshus Sundlisater N, Lillegraven S, Sexton J, Bugge Nordberg LB, et al. (2022) Fatigue in patients with early rheumatoid arthritis undergoing treat-to-target therapy: predictors and response to treatment. Ann Rheum Dis 81(3): 344-350.
29. Versteeg GA, ten Klooster PM, van de Laar MAFJ (2022) Fatigue is associated with disease activity in some, but not all, patients living with rheumatoid arthritis: disentangling "between-person" and "within-person" associations. BMC Rheumatol 6: 3.
30. Kristensen LE, Bliddal H, Christensen R, Karlson JA, Gülfe A, et al. (2014) Is swollen to tender joint count ratio a new and useful clinical marker for biologic drug response in rheumatoid arthritis? Results from a Swedish cohort. Arthritis Care Res 66(2): 173-179.
31. Orucoglu N, Alp A, Yurtkuran DM (2022) Assessment of disease activity with simplified joint ultrasonography method in rheumatoid arthritis patients. J Surg Med 6(6): 623-628.
32. van Campen E, van den Eede F, Moorkens G, Schotte Ch, Schacht, et al. (2009) Use of the Temperament and Character Inventory (TCI) for Assessment of Personality in Chronic Fatigue Syndrome. Psychosomatics 50(2): 147-154.
33. Gökmen F, Altınbaş K, Akbal A, Çelik M, Reşorlu H, et al. (2015) Assessment of temperament and character of rheumatoid arthritis patients. Akt Rheumatol 40(1): 58-61.
34. Gy Kiss E, Csókási K, Hargitai R, Káplár M, Nagy L, et al. (2012) Resilience and protective factors of personality. Psychol Health 27(Suppl 1): 222.
35. Avgoustaki F, Gillibrand R, Flurey C (2015) Examining personality traits, coping styles and adjustment in rheumatoid arthritis patients: A pilot tudy. Rheumatology 54(Suppl 1): i111-i111.
36. Smesam HN, Qazmooz HA, Khayoon SQ, Almulla AF, Al Hakeim HK, et al. (2022) Pathway phenotypes underpinning depression, anxiety, and chronic fatigue symptoms due to acute rheumatoid arthritis: A precision nomothetic psychiatry analysis. J Pers Med 12(3): 476.
37. Uda M, Hashimoto M, Uozumi R, Torii M, Takao Fujii T, et al. (2021) Factors associated with anxiety and depression in rheumatoid arthritis patients: a cross-sectional study. Advances in Rheumatology 61: 65.
38. Ionescu CE, Popescu CC, Agache M, Dinache G, Codreanu C (2022) Depression in rheumatoid arthritis: A narrative review-diagnostic challenges, pathogenic mechanisms and effects. Medicina 58(11): 1637.
39. Gezsi A, Van der Auwera S, Mäkinen H, Eszlari N, Hullam G, et al. (2024) Unique genetic and risk-factor profiles in clusters of major depressive disorder-related multimorbidity trajectories. Nature Communications 15: 7190.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.58.009186

László Hodinka. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php