CAJM

Central Asian Journal of Medicine

100 TMA anniversary

Tashkent Medical Academy Press

eISSN: 2181-1326

Scientific Journal

This journal had been publishing since 2018

10

2025

MINISTRY OF HIGHER AND SECONDARY SPECIALIZED EDUCATION OF THE REPUBLIC OF UZBEKISTAN

2030 UZBEKISTAN RESEARCH ONLINE

OAK.uz Supreme Attestation Commission at the Cabinet Ministers of the Republic of Uzbekistan

Digital Commons Network

Google Scholar

C A J M

Central Asian Journal of Medicine

Tashkent Medical Academy Press

Scientific Journal

This journal had been publishing since 2018

eISSN: 2181-1326 (online)
ISSN: 2181-7812 (print)

№ 10, 2025. Vol. 1

The Central Asian Journal of Medicine is peer-reviewed scientific journal that publishes original scientific articles. The series has been founded at the Tashkent Medical Academy in 2011. The main goal of this scientific journal is to promote the development of education and research work among teachers, doctoral students and students in Medical Sciences, Medical Education, Public Health, Nursing, Rehabilitation and Therapy.

OAK.uz **Supreme Attestation Commission at the Cabinet Ministers of the Republic of Uzbekistan**

CONTENTS OF THE JOURNAL

FATIGUE INDEX IN RHEUMATOID ARTHRITIS: CORRELATION WITH CDAI AND RAPID3

Maruf Anorboev – MD, MSc, Ph.D. researcher
Khalmurad Akhmedov – MD, DSc
Javohir Mullokulov – MD, Ph.D. researcher
Tashkent Medical Academy (Tashkent, Uzbekistan)
mullokulov33@gmail.com

Abstract. Background: *Fatigue is a major and disabling symptom of rheumatoid arthritis (RA), often persisting despite controlled inflammation. Its relationship with composite disease activity indices remains incompletely understood.*

Objectives: *To evaluate the correlation between fatigue and disease activity indices (CDAI and RAPID3) and to identify predictors of fatigue severity in a real-world RA cohort.*

Methods: *A cross-sectional study of 160 RA patients fulfilling 2010 ACR/EULAR criteria was conducted. Fatigue was assessed using the FACIT-F and VAS scales; disease activity by CDAI and RAPID3. Depression (PHQ-9) and sleep quality (PSQI) were included as covariates. Correlations were analyzed using Spearman's coefficient, and multivariable regression identified independent predictors.*

Results: *Mean CDAI and RAPID3 were 17.2 ± 7.6 and 4.9 ± 2.1, respectively; mean FACIT-F was 30.8 ± 8.5. Fatigue correlated strongly with RAPID3 ($\rho = -0.61$, $p < 0.001$) and moderately with CDAI ($\rho = -0.46$, $p < 0.001$). In adjusted models, RAPID3 ($\beta = -0.52$, $p < 0.001$), pain, and depressive symptoms independently predicted fatigue (adjusted $R^2 = 0.584$).*

Conclusions: *Fatigue in RA is multifactorial and correlates more closely with patient-reported indices than with physician-assessed activity, emphasizing the need for holistic, patient-centered management.*

Keywords: *Rheumatoid arthritis; fatigue; CDAI; RAPID3; FACIT-F; patient-reported outcomes; depression; sleep; real-world study.*

Introduction: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and a broad range of extra-articular manifestations [1,2]. While clinical assessment of RA traditionally focuses on objective measures of disease activity—such as swollen and tender joint counts or acute phase reactants—patients frequently report symptoms that extend beyond joint pain and stiffness [3,4]. Among these, fatigue stands out as one of the most prevalent and disabling manifestations of RA, often exceeding pain as a determinant of impaired quality of life. Fatigue in RA is complex and multifactorial, arising from the interplay of systemic inflammation, pain, sleep disturbance, anemia, psychological stress, and treatment effects. Even in patients achieving clinical remission, residual fatigue may persist, suggesting partial independence from inflammatory activity. This disconnect underscores the need to explore fatigue not merely as a secondary symptom but as a core outcome reflecting the patient's overall disease burden. The Outcome Measures in Rheumatology (OMERACT) group has emphasized fatigue as a mandatory patient-reported domain in RA clinical trials, reinforcing its relevance in treat-to-target paradigms [5,6]. Composite indices such as the Clinical Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data 3 (RAPID3) integrate both physician- and patient-reported components to quantify disease activity. While CDAI is weighted toward joint counts and clinician assessment, RAPID3 is entirely patient-driven, incorporating functional status, pain, and global well-being. Given these differing structures, the extent to which fatigue correlates with each index remains uncertain, particularly in real-world clinical settings where psychological and socioeconomic factors may influence patient perception of disease. Understanding the relationship between fatigue and these composite indices is crucial for holistic RA management. If fatigue shows stronger association with patient-reported outcomes such as RAPID3 than with clinician-based scores like CDAI, it may highlight the need to integrate fatigue-targeted interventions—addressing sleep, mood, and lifestyle—alongside anti-inflammatory therapy. Moreover, such insights could help clinicians interpret discordant CDAI–RAPID3 results and tailor treatment approaches to individual patient needs. The present study aimed to assess the correlation between fatigue and composite disease activity indices (CDAI and RAPID3) among patients with RA in a regional real-world cohort. A secondary aim was to determine whether fatigue remains associated with disease activity after adjusting for key modifiers such as pain, depression, and anemia. By elucidating these relationships, this study seeks to clarify the multidimensional nature of fatigue and its potential role as an independent target in RA management [7,8].

Material and Methods: This cross-sectional observational study was conducted at the Department of Internal Diseases, Family Medicine No. 2, Tashkent Medical Academy, and affiliated rheumatology outpatient clinics between January 2023 and July 2024. The study aimed to assess the relationship between fatigue and composite disease activity indices among patients with rheumatoid arthritis (RA) in a real-world clinical setting. A total of 160 adult patients who met the 2010 ACR/EULAR classification criteria for RA were consecutively enrolled during routine visits. Inclusion criteria were age ≥18 years, disease duration of at least six months, and stable therapy with conventional or biological disease-modifying antirheumatic drugs (DMARDs) for at least twelve weeks. Exclusion criteria included other autoimmune diseases, active infection, malignancy, uncontrolled endocrine or psychiatric disorders, fibromyalgia, pregnancy, or lactation. Demographic and clinical data such as age, sex, body mass index, disease duration, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody status, treatment regimen, and comorbidities were recorded. Disease activity was evaluated using the Clinical Disease Activity Index (CDAI) and the Routine Assessment of Patient Index Data 3 (RAPID3). The CDAI was calculated as the sum of the 28-tender joint count (TJC28), 28-swollen joint count (SJC28), patient global assessment (PtGA), and physician global assessment (PhGA), each measured on a 0–10 cm visual analogue scale (VAS). The RAPID3 score was determined as the mean of three patient-reported components: physical function (MDHAQ-FN), pain, and patient global assessment, each rated on a 0–10 scale. Laboratory parameters including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and hemoglobin (Hb) were measured in a single certified laboratory using standardized methods. Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire and a 10-cm fatigue visual analogue scale (VAS). The FACIT-F includes 13 items, each rated on a 5-point Likert scale from 0 (“not at all”) to 4 (“very much”), producing a total score between 0 and 52, where lower scores indicate more severe fatigue. To control for confounding factors, depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9), and sleep quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI), both validated in Uzbek and Russian translations. All questionnaires were self-administered with trained staff assistance when necessary. Statistical analyses were performed using IBM SPSS Statistics version 26.0 and GraphPad Prism version 10.0. Continuous variables were tested for normality using the Shapiro–Wilk test and expressed as mean ± standard deviation (SD) or median (interquartile range), while categorical variables were reported as frequencies and percentages. Correlations between fatigue (FACIT-F and VAS) and disease activity indices (CDAI and RAPID3) were analyzed using Spearman’s rank correlation coefficient (ρ) with 95% confidence intervals. Partial correlations were computed to adjust for potential confounders including pain, depressive symptoms, sleep quality, anemia, and body mass index. Multivariable linear regression models were constructed with fatigue (FACIT-F) as the dependent variable and CDAI or RAPID3 as independent predictors, adjusting for age, sex, disease duration, pain, PHQ-9, PSQI, Hb, and steroid dose. Statistical significance was defined as $p < 0.05$.

Table 1.

Baseline characteristics of patients with rheumatoid arthritis (n = 160)

Characteristic	Value
Age, years (mean ± SD)	52.8 ± 11.6
Female, n (%)	127 (79.4)
Disease duration, years (median [IQR])	8.4 (5.0 – 12.3)
Rheumatoid factor positive, n (%)	119 (74.3)
Anti-CCP positive, n (%)	110 (68.7)
Body mass index, kg/m^2 (mean ± SD)	26.3 ± 4.8
Methotrexate use, n (%)	140 (87.5)
Methotrexate dose, mg/week (mean ± SD)	16.8 ± 5.3
Leflunomide use, n (%)	55 (34.4)
Oral corticosteroid use (≤ 10 mg/day), n (%)	46 (28.8)
Biologic/targeted DMARD use, n (%)	36 (22.5)
CDAI (mean ± SD)	17.2 ± 7.6
RAPID3 (mean ± SD)	4.9 ± 2.1
FACIT-F (mean ± SD)	30.8 ± 8.5
Fatigue VAS (0–10, mean ± SD)	6.2 ± 1.9
PHQ-9 (mean ± SD)	8.7 ± 4.2
PSQI (mean ± SD)	8.1 ± 3.1

BMI – body mass index; CDAI – Clinical Disease Activity Index; RAPID3 – Routine Assessment of Patient Index Data 3; FACIT-F – Functional Assessment of Chronic Illness Therapy–Fatigue; VAS – visual analogue scale; PHQ-9 – Patient Health Questionnaire-9; PSQI – Pittsburgh Sleep Quality Index; DMARD – disease-modifying antirheumatic drug.

Table 2.

Correlation between fatigue scores and disease activity indices in patients with rheumatoid arthritis (n = 160)

Variables Compared	Spearman ρ	p-value	Strength of Correlation*
FACIT-F vs RAPID3	−0.61	< 0.001	Strong negative
FACIT-F vs CDAI	−0.46	< 0.001	Moderate negative
Fatigue VAS vs RAPID3	0.64	< 0.001	Strong positive
Fatigue VAS vs CDAI	0.42	< 0.001	Moderate positive
RAPID3 vs Pain VAS	0.71	< 0.001	Very strong positive
RAPID3 vs Patient Global Assessment (PtGA)	0.67	< 0.001	Strong positive
CDAI vs Swollen Joint Count (SJC28)	0.59	< 0.001	Moderate-strong positive
CDAI vs ESR	0.48	< 0.001	Moderate positive

*ρ: 0.00–0.19 = very weak, 0.20–0.39 = weak, 0.40–0.59 = moderate, 0.60–0.79 = strong, ≥ 0.80 = very strong.

FACIT-F – Functional Assessment of Chronic Illness Therapy–Fatigue; VAS – Visual Analogue Scale; CDAI – Clinical Disease Activity Index; RAPID3 – Routine Assessment of Patient Index Data 3; PtGA – Patient Global Assessment; SJC28 – Swollen Joint Count (28 joints); ESR – Erythrocyte Sedimentation Rate.

Table 3.

Multivariable linear regression analysis with FACIT-F as the dependent variable (n = 160)

Predictor	Standardized β (95% CI)	p-value	Interpretation
RAPID3 (per 1 unit increase)	−0.52 (−0.68 to −0.36)	< 0.001	Strong independent negative association
CDAI (per 1 unit increase)	−0.18 (−0.39 to 0.03)	0.09	Not statistically significant after adjustment
Pain VAS (per 1 unit)	−0.31 (−0.45 to −0.17)	< 0.001	Significant negative predictor
PHQ-9 (per 1 unit)	−0.26 (−0.42 to −0.10)	0.003	Independent contributor to fatigue
PSQI (per 1 unit)	−0.08 (−0.22 to 0.06)	0.27	NS
Hemoglobin (per 1 g/L)	0.04 (−0.06 to 0.14)	0.43	NS
BMI (per 1 kg/m^2)	0.03 (−0.07 to 0.13)	0.56	NS
Steroid dose (per 1 mg/day)	−0.06 (−0.16 to 0.04)	0.24	NS

Discussion: This study demonstrated that fatigue in rheumatoid arthritis (RA) is a multidimensional symptom that correlates more strongly with patient-reported indices such as RAPID3 than with clinician-based disease activity measures like CDAI. Although both indices were significantly associated with fatigue, only RAPID3 remained an independent predictor after controlling for pain, depression, sleep quality, anemia, and corticosteroid use. These findings suggest that the experience of fatigue reflects not only the inflammatory process but also psychosocial and behavioral domains that are captured more effectively by patient-reported outcomes. Fatigue has long been recognized as a major determinant of quality of life in RA and is now considered a core outcome domain in the OMERACT framework and recent EULAR treat-to-target recommendations. However, it is frequently overlooked in daily practice because it is not directly integrated into conventional composite indices such as DAS28 or CDAI. The results of the present study underscore the clinical value of including fatigue assessment in routine disease monitoring, particularly through patient-centered instruments like RAPID3, which encompass pain, function, and global well-being.

The correlation patterns observed in this cohort highlight the conceptual differences between RAPID3 and CDAI. RAPID3 is entirely derived from patient self-assessment, which reflects the subjective burden of symptoms, while CDAI is largely based on joint counts and physician evaluation, emphasizing the inflammatory component of disease. This distinction explains why fatigue correlated more strongly with RAPID3 (ρ = −0.61) than with CDAI (ρ = −0.46). Similar findings have been reported in multicenter studies showing that fatigue aligns more closely with

pain intensity, mood, and functional limitations than with laboratory or joint-based measures of inflammation. These data support the notion that a subset of patients may experience what has been termed "residual fatigue" or "discordant remission," where inflammatory activity is well-controlled but patients continue to experience fatigue, poor sleep, and low vitality. The persistence of fatigue despite clinical remission has been documented in several European and North American cohorts and is increasingly interpreted as an outcome of central sensitization, mood disturbance, and neuroimmune dysregulation rather than active synovitis [9,10]. Mechanistically, fatigue in RA is understood as a neuroimmune phenomenon involving bidirectional signaling between the immune system and the central nervous system. Proinflammatory cytokines such as IL-6, TNF-α, and IL-1β can induce sickness behavior, reduce motivation, and alter hypothalamic–pituitary–adrenal axis function. Neuroimaging studies have shown altered functional connectivity in limbic and prefrontal networks in fatigued RA patients, suggesting that chronic inflammation can reprogram neural circuits related to energy and attention [11,12]. Nonetheless, the persistence of fatigue in patients with low inflammatory markers points to a broader biopsychosocial model where pain, depression, physical inactivity, and poor sleep reinforce one another in a self-sustaining cycle. In this context, our observation that depressive symptoms and pain were strong independent predictors of fatigue is highly consistent with previous meta-analyses and registry data, which indicate that psychological distress and pain explain more variance in fatigue than inflammatory activity alone. This finding further justifies the integration of psychosocial interventions, physical exercise, and cognitive-behavioral strategies alongside pharmacologic disease control [13,14].

From a global perspective, the mean FACIT-F score in this Uzbek cohort (30.8 ± 8.5) reflects a moderate-to-severe level of fatigue comparable to values reported in European registries, but slightly lower than in biologic-treated populations, where mean scores exceed 35. This likely reflects limited access to biologic and targeted synthetic DMARDs in lower-resource settings, leading to higher corticosteroid dependence and persistent low-grade inflammation. Only 22.5% of patients in this study received biologic therapy, compared with over 60% in Western cohorts, emphasizing disparities in therapeutic accessibility that may exacerbate fatigue burden. These data therefore contribute valuable regional evidence from Central Asia, a setting underrepresented in global rheumatology research, and highlight the socioeconomic and healthcare system factors that influence patient outcomes beyond biological disease activity.

Clinically, these findings carry several implications. Fatigue should be routinely assessed using validated instruments such as FACIT-F or a simple fatigue VAS. When patients report high fatigue despite low CDAI, clinicians should investigate non-inflammatory contributors, including pain, depressive symptoms, and sleep disturbance, rather than automatically escalating immunosuppressive therapy. The inclusion of fatigue measures in electronic health systems or outpatient records would allow for longitudinal tracking and earlier recognition of "discordant remission" cases. Moreover, incorporating fatigue assessment into treat-to-target strategies would enhance alignment between physician and patient priorities, fostering shared decision-making and holistic management. The study also opens important avenues for future research. Longitudinal studies are needed to assess whether changes in fatigue parallel improvements in disease activity or whether they follow independent trajectories. Biomarker-based studies could clarify whether specific cytokine profiles (e.g., IL-6, IL-18, TNF-α, MMP-9) are associated with fatigue severity, helping distinguish inflammatory from non-inflammatory fatigue phenotypes. In addition, interventional trials combining anti-inflammatory therapy with exercise or cognitive-behavioral interventions could evaluate integrated approaches to fatigue reduction [15]. Establishing regional fatigue registries would enable comparative studies between different socioeconomic environments and provide real-world data on patient-reported outcomes across diverse healthcare systems. Despite its strengths, including a standardized evaluation framework and comprehensive adjustment for confounders, this study has some limitations. Its cross-sectional design precludes causal inference, and fatigue, depression, and sleep quality were self-reported, which may introduce recall bias. Biological markers of inflammation were limited to ESR and CRP, precluding deeper mechanistic insights. Nonetheless, the consistency of results across multiple analyses supports the robustness of the observed associations.

In summary, the present study confirms that fatigue in rheumatoid arthritis is not merely a byproduct of inflammation but a complex, multidimensional construct encompassing biological, psychological, and behavioral determinants. The stronger association of fatigue with RAPID3 than with CDAI highlights the value of patient-reported indices in capturing the lived experience of disease. Effective management of RA should therefore combine pharmacologic disease control with interventions targeting pain, mental health, and sleep to address fatigue as a central component of patient well-being. Recognizing fatigue as a treatable and measurable outcome is essential for achieving true remission—not only in joints, but in patients' lives.

Disclosure of interest: The authors declare no conflicts of interest related to this study. No financial support, sponsorship, or grants were received from pharmaceutical companies, medical device manufacturers, or commercial entities for the conduct of this research. All authors were involved in the conception, data collection,

analysis, and manuscript preparation independently and take full responsibility for the integrity of the data and the accuracy of the analysis.

Funding Statement: This research was conducted without external funding. All study procedures, data collection, and analyses were supported by institutional resources from the Tashkent State Medical University. No grants or financial contributions were received from governmental, industrial, or commercial entities.

Acknowledgments: The authors sincerely thank the Department of Internal Diseases at Family Medicine No. 2, Tashkent State Medical University, for providing institutional support and clinical infrastructure for the study. Special gratitude is extended to all participating patients for their trust, cooperation, and valuable contribution to this research.

REFERENCES

1. Aletaha D, Smolen JS. The simplified disease activity index (SDAI) and the clinical disease activity index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol.* 2019;37(Suppl 118):S125–S130.
2. Chandran V, Bhella S, Schentag C, Gladman DD. Functional Assessment of Chronic Illness Therapy–Fatigue scale is valid in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2019;71(10):1320–1328.
3. Choy EH, Calabrese LH. Neuroendocrine and neurophysiological mechanisms of fatigue in rheumatoid arthritis. *Nat Rev Rheumatol.* 2018;14(9):509–520.
4. EULAR Task Force. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological DMARDs: 2023 update. *Ann Rheum Dis.* 2023;82(9):1121–1134.
5. Hewlett S, Chalder T, Choy EH, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology (Oxford).* 2020;59(Suppl 5):v35–v42.
6. Johns N, Taylor PC, Lee YC. Understanding residual fatigue in rheumatoid arthritis: a pathophysiological and clinical perspective. *RMD Open.* 2022;8(2):e002372.
7. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford).* 2016;55(12):2136–2148.
8. Michaud K, Pope J, Emery P. Fatigue in rheumatoid arthritis: biological underpinnings and clinical implications. *Arthritis Rheumatol.* 2020;72(12):1971–1981.
9. OMERACT Fatigue Working Group. Identification of fatigue domains in rheumatoid arthritis: report from the OMERACT 2021 consensus. *J Rheumatol.* 2021;48(9):1392–1400.
10. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology (Oxford).* 2019;58(2):208–215.
11. Schrepf A, Kaplan CM, Ichesco E, et al. A multimodal MRI study of the central nervous system in fatigue associated with rheumatoid arthritis. *Nat Commun.* 2018;9(1):2343.
12. Studenic P, Smolen JS, Aletaha D. Discrepancies between patients and physicians in perception of rheumatoid arthritis disease activity: association with patient outcomes. *Ann Rheum Dis.* 2021;80(11):1431–1437.
13. Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M. A structured literature review of the burden of fatigue and unmet needs among patients with rheumatoid arthritis. *Int J Rheum Dis.* 2020;23(10):1532–1544.
14. van Tuyl LHD, Hewlett S, Sadlonova M, et al. The patient perspective on fatigue in rheumatoid arthritis: qualitative research findings. *RMD Open.* 2021;7(1):e001536.
15. Zautra AJ, Fasman R, Parish BP, Davis MC. Daily fatigue in rheumatoid arthritis: predictors and within-person processes. *Pain.* 2019;160(2):336–344.
16. Anorboyev Maruf Kholbuta ugli, et al. Rheumatoid arthritis: new treatment approaches - a comparative evidence review/ https://tbcenter.uz/ 8 (№13) 2025
17. Mullokulov Javohir et al. Comparative efficacy and safety of baricitinib plus sulfasalazine versus TNF-α inhibitors and sulfasalazine monotherapy in reactive arthritis: a 12-month randomized study/ https://tbcenter.uz/ 8 (№13) 2025
18. Mullokulov Javohir et al. Dynamics of serum anxa1 levels during treatment with baricitinib and sulfasalazine/ journals.tma.uz № 8, 2025. Vol. 1