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Original article

# High prevalence of fatigue in patients with Takayasu arteritis: a case–control study in a Brazilian centre

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## Abstract

**Objectives.** Several studies have shown not only a high prevalence of fatigue but also a reduction in health-related quality of life (HRQoL) in patients with rheumatic diseases. Owing to insufficient research in this area, we aimed to assess the prevalence of fatigue and its contribution to impairment of HRQoL in patients with Takayasu arteritis (TAK).

**Methods.** This single-centre case–control study included 53 TAK patients who were matched by age, BMI and sex with 100 healthy individuals. Aside from the patients' general data, the following information was collected: disease activity, level of activities of daily living (HAQ), physical activity levels and chronic fatigue.

**Results.** The TAK patients and healthy individuals were comparable in terms of current age, BMI and sex distribution. The median disease duration of TAK was 13.0 (7.0–20.0) years, and 11 (20.8%) patients had active disease. Compared with healthy individuals, patients with TAK had a higher prevalence of fatigue and lower HAQ score, physical activity level and intensity, and physical and psychosocial domains of the modified fatigue impact scale ($P < 0.01$). Moreover, TAK patients had increased fatigue rates compared with the healthy individuals (fatigue severity scale: odds ratio = 2.6; 95% CI = 1.2, 5.4; modified fatigue impact scale: odds ratio = 2.6; 95% CI = 1.2, 5.5). Fatigue was positively correlated with worsening HAQ, CRP levels, daily prednisone dose and disease activity, and negatively correlated with disease duration.

**Conclusion.** TAK patients have a higher prevalence of fatigue, which affects different aspects of the disease, including physical function. Thus, fatigue-focused treatments should also be considered in clinical practice.

**Trial registration.** The Brazilian Clinical Trials Registry (ReBEC), https://ensaiosclinicos.gov.br/, RBR-9n4z2hh.

CLINICAL SCIENCE

## Lay Summary

### What does this mean for patients?

Takayasu arteritis is a systemic autoimmune disease that affects blood vessels and causes a variety of symptoms, including pain and fatigue. These symptoms are often overlooked by rheumatologists and health-care professionals. However, 60% of the patients evaluated in this study had fatigue, in addition to being ∼2.6 times more likely to have fatigue than the population without rheumatic disease. On a day-to-day basis, this represents an increase in the difficulty of performing simple tasks, such as taking care of their own home and maintaining self-care, and often makes it difficult for patients to have a social life. This work is focused on fatigue and demonstrates that patients' common complaints cannot be seen as merely tiredness or laziness; we should understand this complaint as important and

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relevant to the lives of patients, even in patients with no disease activity. Patients should seek strategies to combat or prevent this symptom, such as physical activity, because this is a low-cost strategy.

**Key words:** chronic fatigue syndrome, health-related quality of life, systemic vasculitis, Takayasu arteritis

**Key Messages**

- Approximately two-thirds of Takayasu arteritis patients experience chronic fatigue.
- Takayasu arteritis patients have a 2.6 times higher fatigue rate than healthy individuals.
- Non-pharmacological therapies and strategies should be considered to address chronic fatigue in Takayasu arteritis patients.

## Introduction

Chronic fatigue (CF) has been observed in several autoimmune rheumatic diseases, affecting 50–90% of patients; however, it varies considerably among diseases [1]. CF is a persistent and multidimensional symptom that defines the feeling of indisposition and tiredness with no improvement with rest, compromising patients' health-related quality of life (HRQoL) and disease status, such as that seen in autoimmune rheumatic diseases [1, 2]. Currently, no biomarker or laboratory test has been used to assess CF, considering the multidimensional factors of this symptom. In this context, CF has been evaluated using self-reported and validated questionnaires [3]. Moreover, previous studies have shown a high prevalence of CF in patients with systemic vasculitis, consequently compromising the patients' HQRoL and overall disease status [4, 5].

Takayasu arteritis (TAK) is a primary systemic vasculitis that mainly affects young women and causes impairment of large vessels and their main branches (e.g. stenosis and aneurysms) [6]. Studies have demonstrated that patients with TAK have worsened HRQoL, in addition to decreased physical function and physical activity [7, 8]. However, the potential effect of CF on physical function by reducing physical activity levels and influencing disease parameters in patients remains unclear.

In this context, the first aim of this study was to assess the prevalence of CF and its effects on the HRQoL of patients with TAK and compare them with those of volunteers without rheumatic disease. Second, we aimed to evaluate possible associations that might be influenced by CF.

## Methods

### Study design

This was a case–control study carried out in 2020–2021, in a tertiary Brazilian hospital where TAK patients who fulfilled the classification criteria of the ACR were evaluated [9]. We collected clinical data before and during consultations using a standardized clinical form, with the participation of rheumatologists.

Additionally, volunteers without rheumatic diseases were also evaluated in the control (CTR) group; these hospital employees or family members of patients, who were matched to the TAK group by BMI, sex and age.

### Inclusion criteria for TAK and CTR groups

To participate in the study, individuals must have been able to understand and sign the informed consent form and be older than 18 years.

### Exclusion criteria for TAK and CTR group

Individuals who met the classification criteria for FM according to the 1990 ACR were excluded [10]. Patients with long-term coronavirus disease 2019 (COVID-19) were excluded from the study. Additionally, patients who were using drugs with an action on the CNS and factors that could compromise the analyses were excluded. Individuals diagnosed with rheumatic disease or long-term COVID-19 were excluded from the CTR group.

### Questionnaires and assessments

The following information was also collected for each participant: current age, ethnicity, marital status, disease duration, sex, body mass and height, hence BMI; disease duration, serum CRP levels, ESR and disease activity [using the Indian Takayasu clinical activity score (ITAS2020), considering disease activity when $\geq$2 points] [11, 12]; results from the international physical activity questionnaire, short form (IPAQ-SF) [13], HAQ [14, 15], visual analog scale, fatigue (VASf) [3] and the fatigue severity scale (FSS), considering CF when the score was $\geq$36 points [16, 17]; modified fatigue impact scale (MFIS) [18, 19], considering CF when the score was $\geq$38 points, with all questionnaires in the Brazilian-Portuguese language version; and information on physical activity (based on the IPAQ questionnaire) [13].

### Ethical approval

The study was conducted according to the principles of the Declaration of Helsinki [20] and approved by Research Ethics Committee Clinical Hospital of Faculdade de

Medicina da Universidade de Sao Paulo (# 4.565.400) and Plataforma Brasil (CAAE # 41762820.1.0000.0068). All patients signed an informed consent form. The study was written and supervised according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

### Statistical analyses

Quantitative variables were expressed as the mean and S.D. or median and interquartile range, whereas qualitative variables were expressed as the count or frequency (percentage). Regarding inferential statistics, the normality of the data was verified using the Shapiro–Wilk test and graphically using probability density function analysis. To compare quantitative variables between the two groups (TAK *vs* CTR), we used Welch's *t*-test for data that met the normality assumptions or the Wilcoxon–Mann–Whitney test when these assumptions were not met. The association between qualitative variables was assessed using the $\chi^2$ test or Fisher's exact test, according to the distribution and assumptions for use. Additionally, the odds ratio (OR) and 95% CI of each evaluated association were described. Correlations between variables and concordance among the fatigue questionnaires were also tested using Pearson's correlation coefficient (*r*) and Spearman's rank correlation test (rho). Moreover, the correlations were classified according to small ($<0.29$), medium (0.30–0.80) and large ($>0.80$) effect sizes. We considered the OR effect sizes as small when between 0 and 1.50, medium when between 1.51 and 3.00, and large when $>3.00$ [21]. The effect size for the Wilcoxon–Mann–Whitney test was calculated from the effect size *r*, which consisted of the *Z*-statistic divided by the square root of the sample size (*N*) ($Z/\sqrt{\{N\}}$). The interpretation of values for *r* was: 0.10 to $<0.3$, small effect; 0.30 to $<0.5$, moderate effect; and $\geq 0.5$, large effect. Calculations were performed using the *rstatix* package v.0.7.0 in R.

The null hypothesis was rejected when $\alpha$ $P < 0.05$, therefore, were considered statistically significant [22]. Statistical analyses were performed using R v.4.1.2, for Windows (R Core Team, Vienna, Austria) [23].

### Sample size

For our calculations, we considered the sample size necessary to find the difference between the means of two independent groups (*t*-test); therefore, we considered an effect size of 0.5 (medium), a value of $\alpha < 0.05$, with power $(1 - \beta)$ of 0.8, and allocation into two groups with a ratio of 2:1. With these data, we needed samples of 48 and 96 volunteers, in the TAK and CTR groups, respectively. The sample size was calculated using G*Power v.3.1.9.6. for Windows (University of Kiel, Germany) [24].

## Results

Fifty-three TAK patients were selected, along with 100 CTR volunteers, matched by sex, age and BMI. The TAK group had similar marital status to the CTR group ($P > 0.05$); however, the TAK group differed in ethnicity from the CTR group, in which 72% of participants self-classified as White (Table 1).

Approximately 20% of the patients had disease activity according to the ITAS2010 questionnaire. CRP and ESR levels in the TAK group were considered low for the evaluated age range and population (Table 1). Glucocorticoids (prednisone) were used by 23% of the patients. Additionally, 58% of the patients used one or more immunosuppressive drugs, with MTX being the most common drug, followed by AZA (Table 1). Sixty-two per cent of the TAK group had low levels of physical activity, which was significantly different from the CTR group ($P < 0.001$), which also had a low prevalence of participants with high levels of physical activity. The TAK group presented reduced weekly metabolic equivalents ($P < 0.001$). However, the two groups were similar in terms of weekly sedentary time (Table 1).

Patients with TAK demonstrated increased HAQ scores, with a large magnitude of effect of inference between groups, and statistical differences were also found in relationship to the FSS and MFIS questionnaires; however, only the physical domain of the MFIS questionnaire had a moderate effect size for the difference between groups, as shown in Table 2 and Fig. 1.

When evaluated in relationship to obesity (BMI $\geq$ 30 kg/m$^2$), both groups presented similar results ($P > 0.05$) (Table 3).

Agreement among the tools was evaluated using the presence of CF in both groups (MFIS, FSS and VASf), with a medium effect size among the tools, as shown in Fig. 2, with the exception of the correlation between the psychosocial domain (MFIS) and the FSS score, which showed a small effect size (Fig. 2D). All correlations were statistically significant ($P < 0.001$).

Regarding CF, TAK patients presented ~60% prevalence in both questionnaires (FSS and MFIS). Additionally, CF (FSS and MFIS) were significantly associated with the presence of TAK ($P < 0.001$). No other associations were found between the disease-related factors or habits and CF (Table 3).

Correlations between FSS scores and disease duration, weekly metabolic equivalents and prednisone use were classified as weak. However, the FSS score showed a moderate correlation with HAQ and CRP levels. As for the MFIS questionnaire, we found a moderate correlation with the HAQ score and prednisone use ($P < 0.05$). All data are shown in Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online.

Finally, TAK patients showed an OR of fatigue 2.6 times that of the CTR group, with a medium effect size (Table 4).

## Discussion

To the best of our knowledge, this is the first case–control study to assess the prevalence of CF in a significant sample of patients with TAK, comparing it with a sample from the CTR group with a larger sample size. We

**Table 1** Demographic features, disease status, physical activity and drug treatment of patients with Takayasu arteritis and the control group

| Parameter | TAK ($n = 53$) | CTR ($n = 100$) | *P*-value |
|---|---|---|---|
| Age, years | 43.0 (39.0–51.0) | 49.0 (38.0–55.2) | 0.541 |
| Disease duration, years | 13.0 (7.0–20.0) | – | – |
| BMI, kg/m$^2$ | 26.7 (23.0–28.9) | 24.7 (22.3–29.7) | 0.425 |
| Sex (female), *n* (%) | 49 (92.4) | 92 (92.0) | >0.999 |
| Ethnicity (White), *n* (%) | 28 (52.8) | 72 (72.0) | 0.028 |
| Marital status (married), *n* (%) | 24 (45.3) | 49 (49.0) | 0.789 |
| Disease status | | | |
| ITAS2010 (disease activity), *n* (%) | 11 (20.7) | – | – |
| Acute-phase reactants | | | |
| ESR, mm/first h | 15.0 (9.0–25.0) | – | – |
| CRP, mg/l | 3.2 (1.3–5.3) | – | – |
| Physical activity (IPAQ-SF) | | | |
| Low, *n* (%) | 33 (62.3) | 30 (30.0) | <0.001 |
| Moderate, *n* (%) | 15 (28.3) | 33 (33.0) | 0.680 |
| High, *n* (%) | 5 (9.4) | 37 (37.0) | <0.001 |
| Metabolic equivalent, MET/week | 756.0 (396.0–1360.0) | 1707.0 (672.7–3546.0) | <0.001 |
| Sedentary behaviour, h/day | 3.25 (0.0–6.0) | 4.0 (2.0–6.0) | 0.400 |
| Prednisone | | | |
| Current use, *n* (%) | 12 (22.6) | – | – |
| Dose, mg/day | 0.0 (0.0–0.0) | – | – |
| Immunosuppressive drugs | | | |
| Current use of one or more, *n* (%) | 31 (58.5) | – | – |
| AZA, *n* (%) | 10 (18.9) | – | – |
| MTX, *n* (%) | 15 (28.3) | – | – |
| MMF, *n* (%) | 3 (5.7) | – | – |
| LEF, *n* (%) | 4 (7.5) | – | – |
| Infliximab, *n* (%) | 6 (11.3) | – | – |
| Tocilizumab, *n* (%) | 2 (3.8) | – | – |

Data are presented as the median (interquartile range) or number (percentage). Statistical significance was determined at a *P*-value of <0.05. CTR: control group; ITAS2010: Indian Takayasu clinical activity score; MET: Metabolic equivalent; TAK: Takayasu arteritis.

**Table 2** Chronic fatigue and level of activities of daily living of patients with Takayasu arteritis

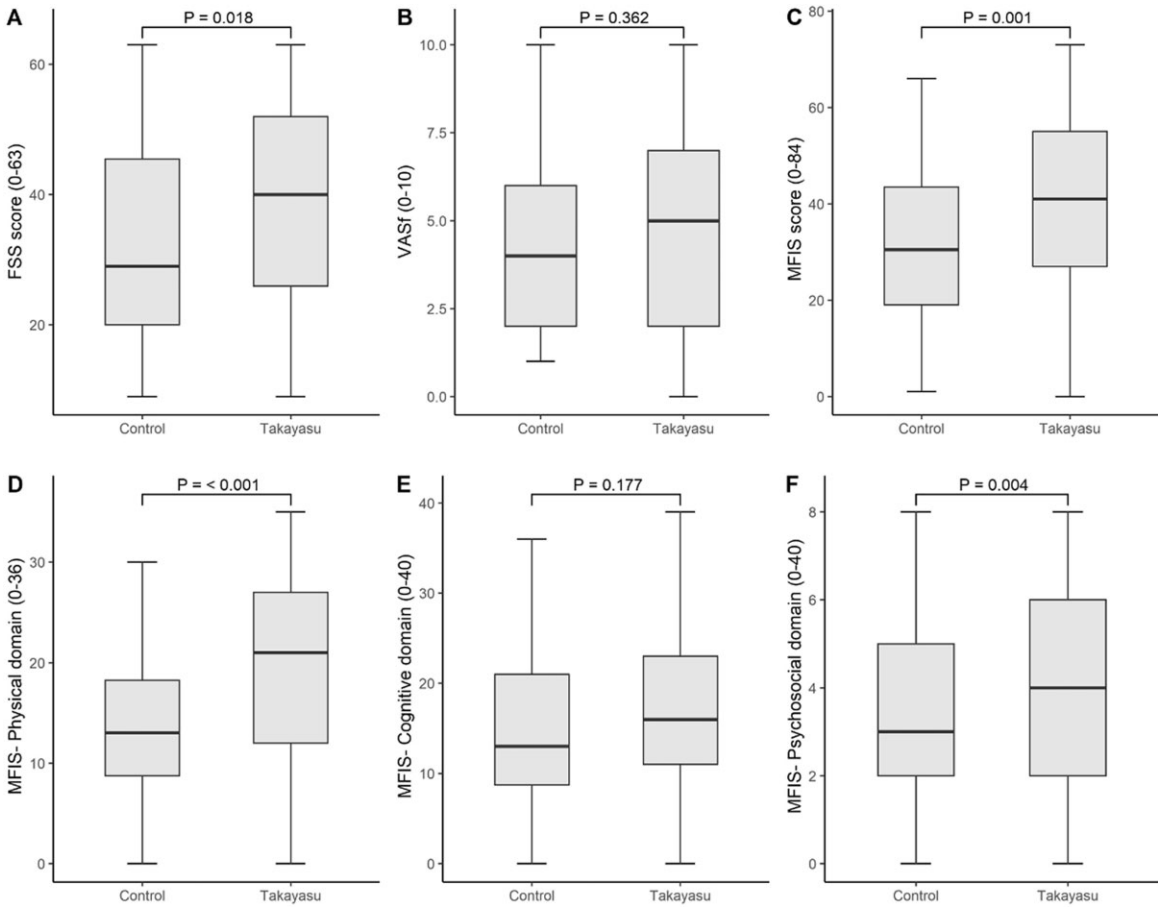
| Score | TAK ($n = 53$) | CTR ($n = 100$) | *P*-value | Effect size | | |
|---|---|---|---|---|---|---|
| | | | | *r* | 95% CI | Magnitude |
| HAQ (0.00–3.00) | 0.62 (0.25–1.00) | 0.00 (0.00–0.12) | <0.0001 | 0.557 | (0.42, 0.67) | Large |
| FSS score (0–63) | 40.00 (26.00–52.00) | 29.00 (20.00–45.50) | 0.018 | 0.191 | (0.03, 0.35) | Small |
| VASf (0–10) | 5.00 (2.00–7.00) | 4.00 (2.00–6.00) | 0.362 | 0.074 | (0.00, 0.24) | Small |
| MFIS total score (0–80) | 41.00 (27.00–55.00) | 30.5 (19.00–43.50) | 0.001 | 0.264 | (0.10, 0.42) | Small |
| MFIS physical domain (0–36) | 21.00 (12.00–27.00) | 13.00 (8.75–18.25) | <0.001 | 0.355 | (0.19, 0.49) | Moderate |
| MFIS cognitive domain (0–40) | 16.00 (11.00–23.00) | 13.00 (8.75–21.00) | 0.177 | 0.109 | (0.01, 0.27) | Small |
| MFIS psychosocial domain (0–8) | 4.00 (2.00–6.00) | 3.00 (2.00–5.00) | 0.004 | 0.233 | (0.07, 0.39) | Small |

Data are presented as the median (interquartile range). Statistical significance was determined at a *P*-value of <0.05. CTR: control group; FSS: fatigue severity scale; MFIS: modified fatigue impact scale; *r*: effect size for the Wilcoxon–Mann–Whitney test; TAK: Takayasu arteritis; VASf; visual analog fatigue scale.

demonstrated a 2.6-fold increase in the prevalence of CF, which compromised the patients' HRQoL and was shown to be reduced through HAQ with a large magnitude of effect, in the TAK group compared with that in the CTR group. Moreover, we evaluated possible clinical correlations and associations between clinical characteristics and CF, presenting a significant sample comparable to the CTR group, which was matched to TAK patients in terms of BMI, sex and age.

We excluded patients and CTR participants diagnosed with FM because FM could compromise our analyses owing to the high prevalence of CF in this

FIG. 1 Comparison of chronic fatigue between Takayasu arteritis patients and the control group




FSS: fatigue severity scale; MFIS: modified fatigue impact scale; VASf: visual analog scale to evaluate fatigue severity. Statistical significance was determined at a *P*-value of $<0.05$.

population [25]. This exclusion was enforced by doctors who were diagnosed with FM and met the ACR criteria of 1990 [10].

Considering the possibility of interference from long-term COVID-19 syndrome, we did not include these patients in our CTR group during the selection process. Additionally, we highlight the early and priority vaccination at our centre for patients with autoimmune diseases (including TAK), the vaccination programme that took place months before the vaccination of the healthy population (CTR group) in Brazil. Therefore, from this assumption, it is possible that the CTR group would suffer more effects from COVID-19 infection in terms of frequency and intensity; for example, fatigue. However, our data show the opposite result, which highlights our finding.

In agreement with the results of other studies [7, 8], our TAK group showed a reduction in the ability to perform activities of daily living (e.g. an increase in the HAQ score), which might represent a reduction in the quality of life of this population. This increase in HAQ scores might also interfere with the physical activity level of this population through a vicious circle that leads secondarily to a reduction in weekly caloric expenditure and, ultimately, favours the presence of other co-morbidities and modifiable cardiovascular risk factors. An example of a factor that could interfere with fatigue and cytokine levels, obesity, did not present a statistically significant difference between the groups; thus, it did not appear to be a confounding factor in our study. In this regard, we also emphasize evaluation group matching [26].

TAK patients showed increased CF compared with the CTR group in both the FSS and MFIS questionnaires. Fatigue is well documented in other diseases, such as RA, multiple sclerosis, chronic obstructive pulmonary disease, SLE and cancer, which are common in chronic diseases [27, 28]. As proposed by Davies *et al.* [29], fatigue has multifactorial characteristics in rheumatic diseases, and its onset is influenced by physiological, psychological, socio-cultural and temporal autoimmune factors, along with possible interference from autoimmune inflammatory factors.

As in other studies, we hypothesized the onset to be related to patient exposure to a prolonged increase in

**Table 3** Association between the presence of chronic fatigue and possible related factors in patients with Takayasu arteritis

| | TAK ($n = 53$) | | Odds ratio | 95% CI | *P*-value |
|---|---|---|---|---|---|
| | Presence | | | | |
| | Count | Percentage | | | |
| **FSS** | 33 | 62.3 | – | – | – |
| Chronic fatigue by MFIS | 31 | 58.5 | 10.5 | (2.6, 51.6) | <0.001 |
| Ethnicity (White) | 28 | 52.8 | 0.6 | (0.2, 2.1) | 0.545 |
| Sex (female) | 49 | 92.4 | 0.6 | (0.0, 8.7) | 0.627 |
| Disease activity (ITAS2010) | 11 | 20.7 | 8.0 | (1.0, 376.3) | 0.063 |
| Use of prednisone | 12 | 22.6 | 2.1 | (0.4, 13.8) | 0.500 |
| Use of immunosuppressive drugs | 31 | 58.5 | 0.9 | (0.2, 3.2) | >0.999 |
| Use of statins | 33 | 62.3 | 1.7 | (0.4, 6.8) | 0.597 |
| Obesity (BMI $\geq$ 30 kg/m$^2$) | 11 | 20.7 | 0.7 | (0.1, 3.3) | 0.728 |
| Low physical activity (IPAQ-SF) | 33 | 62.3 | 1.2 | (0.3, 4.2) | >0.999 |
| **MFIS** | 31 | 58.5 | – | – | – |
| Chronic fatigue by FSS | 33 | 62.3 | 10.5 | (2.6, 51.6) | <0.001 |
| Ethnicity (White) | 28 | 52.8 | 2.1 | (0.6, 7.6) | 0.294 |
| Sex (female) | 49 | 92.4 | 0.2 | (0.0, 2.9) | 0.217 |
| Disease activity (ITAS2010) | 11 | 20.7 | 4.0 | (0.7, 42.3) | 0.097 |
| Use of prednisone | 12 | 22.6 | 4.6 | (0.8, 48.7) | 0.093 |
| Use of immunosuppressive drugs | 31 | 58.5 | 1.8 | (0.5, 6.4) | 0.439 |
| Use of statins | 33 | 62.3 | 1.9 | (0.5, 7.8) | 0.431 |
| Obesity (BMI $\geq$ 30 kg/m$^2$) | 11 | 20.7 | 0.3 | (0.1, 1.5) | 0.168 |
| Low physical activity (IPAQ-SF) | 33 | 62.3 | 0.6 | (0.2, 2.3) | 0.645 |

Statistical significance was determined at a *P*-value of <0.05. CTR: control group; FSS: fatigue severity scale; IPAQ-SF: the international physical activity questionnaire, short form; ITAS2010: Indian Takayasu clinical activity score; MFIS: modified fatigue impact scale; TAK: Takayasu arteritis.

the expression of IL-6 and IL-1 cytokines, and in cancer, which is common in the inflammatory process of vasculitis and, specifically, of TAK. However, our analysed patients had similar normality values, in view of the reduced value of CRP; that is, most of our patients were in disease remission [30, 31].

Corroborating our findings, Druce *et al.* [32] showed that patients with RA, even those in clinical remission, had high CF values, indicating that regardless of the initial triggers, disease remission is unrelated to CF remission. This association demonstrates the interference of additional mechanisms in the maintenance of fatigue. Furthermore, in patients with ANCA-associated vasculitis, the data demonstrated that inflammation plays a minor role in the maintenance of fatigue [33].

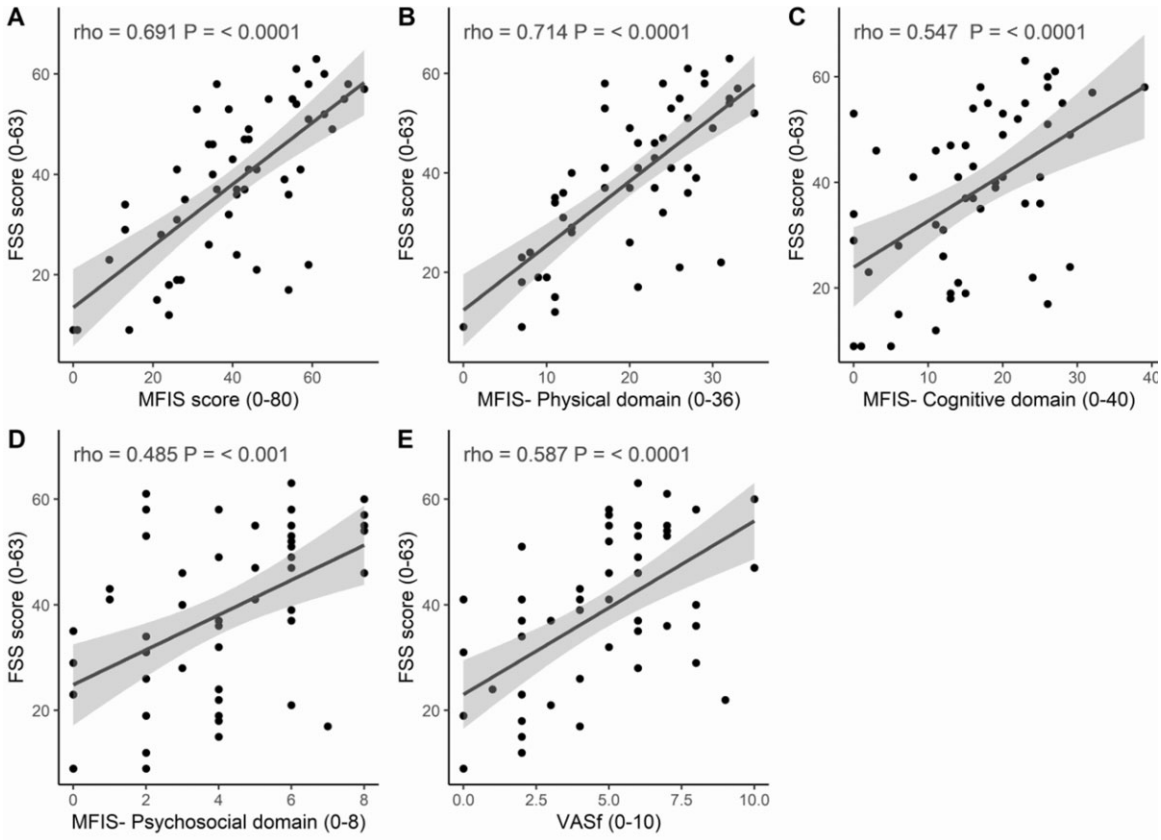
Psychological factors can also interfere with the origin of fatigue. Pust *et al.* [34] demonstrated that psychological trauma in childhood can interfere with the perception of CF in patients with multiple sclerosis as a defence mechanism, leading to the assumption that the trauma of the diagnosis or the initial phase of TAK might increase the perception of CF in these patients, possibly by CNS mechanisms found in chronic pain.

Similar to chronic pain, CF has a central sensitization mechanism, possibly triggering the inflammatory phases of the disease, but remaining maladaptive, as seen in the patients evaluated in this study [35]. However, the possible relationships between the prevalence of fatigue and chronic pain, in addition to sleep disturbances, were not evaluated in the present study, limiting further analysis.

According to Noakes *et al.* [36], peripheral (muscle) and CNS fatigue mechanisms occur together, in a feedback process, with the objective of maintaining homeostasis, especially in activities that can lead to considerable damage to the body. This mechanism is known as the central governor model. In a simple way, the central governor model can explain fatigue as a process of maladaptive modulation of the central drive, aimed at preventing the process of possible damage related to the disease's inflammatory phases, but failing to return to the initial (healthy) pattern [37].

Regardless of the mechanism or the possible complexity of the possible explanations, our patients presented a reduction in HRQoL evaluated using the HAQ. In our study, this reduction was correlated with CF, leading us to consider fatigue an important factor related to the impairment of patients' HRQoL. Furthermore, the duration (e.g. chronicity) of the disease and CRP were correlated with the presence of fatigue, which reinforces the relationship between the inflammatory process, specifically IL-6, and this symptom; however, TAK demonstrates a low level of disease activity and low values of acute-phase reactants.

FIG. 2 Spearman rank correlation coefficient between chronic fatigue assessment tools




FSS: the fatigue severity scale; MFIS: modified fatigue impact scale; rho: Spearman's rank correlation coefficient; VASf: visual analog scale to evaluate fatigue severity. Statistical significance was determined at a *P*-value of $<0.05$.

TABLE 4 Odds ratio for the presence of chronic fatigue and diagnosis of Takayasu arteritis

| | TAK ($n = 53$) | | CTR ($n = 100$) | | Odds ratio | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|
| Presence of chronic fatigue | Count | Percentage | Count | Percentage | | | |
| Chronic fatigue assessed by FSS | 33 | 62.3 | 39 | 39.0 | 2.6 | (1.2, 5.4) | 0.010 |
| Chronic fatigue assessed by MFIS | 31 | 58.5 | 35 | 35.0 | 2.6 | (1.2, 5.5) | 0.009 |

Statistical significance was determined at a *P*-value of $<0.05$. CTR: control group; FSS: fatigue severity scale; MFIS: modified fatigue impact scale; TAK: Takayasu arteritis.

The positive correlation between prednisone dosage and fatigue might suggest that patients with higher doses are more prone to CF; however, most of the patients evaluated were using low doses of prednisone. In contrast to our results, studies in advanced cancer populations have shown that the use of CSs can reduce CF; however, these findings remain debateable. Considering the multifactorial process of fatigue and the fact that several side effects can be attributed to CSs, their prescription and maintenance must be evaluated with caution. Moreover, it is crucial to interpret the prolonged use of these drugs to relieve these chronic symptoms [38, 39].

Because of the widespread occurrence of CF impairment and the possible side effects of available drugs, non-pharmacological treatment, specifically physical training, can be an excellent strategy for CF treatment in TAK, as observed in other conditions [40]. Furthermore, physical training can have the additional effect of improving modifiable cardiovascular risk

factors, such as low physical activity levels and reduced weekly metabolic equivalents, thus improving the patients' HRQoL in a systemic way [41].

Other tools that focus on CNS desensibilization, such as non-invasive central electrostimulation, show potential in the treatment of this condition [42].

The moderate effect size found when comparing the physical domain of the MFIS between the groups led us to believe that these patients were mainly affected physically by fatigue, confirming decreases in the level of physical activity and activities of daily living (HAQ), ultimately leading to the worsening of health overall. However, even with differences in the results in the other domains of the MFIS and FSS, the patients showed small magnitudes of effect. Further investigations to understand the need for fatigue and how it affects rheumatic patients and specifically patients with TAK.

Alarmingly, patients with TAK presented 2.6 times more fatigue than members of the CTR groups, indicating a possible link between TAK and fatigue. As demonstrated in this study, health professionals should encourage non-pharmacological treatments, such as physical training, and emphasize multidisciplinary treatment, especially when considering patients' reports on CF symptoms.

### Conclusions

The TAK patients in our study had a reduced level of HRQoL, in addition to a reduced level and intensity of physical activity, possibly related to CF. Multidisciplinary and non-pharmacological therapies that make it possible to improve fatigue result in a general improvement in the disease and HRQoL.

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*Disclosure statement:* The authors have declared no conflicts of interest.

## Data availability statement

All data relevant to the study are included in the article. The data underlying this article will be shared on reasonable request to the corresponding author.

## Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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