SHORT COMMUNICATION

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Depression as a major determinant of PASS (Patient's Acceptable Symptoms State) in rheumatoid arthritis: a cross-sectional study in Brazilian patients

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease with profound repercussions on the patient's well-being. Chronic pain, restriction of activities, and fatigue after the chronic articular inflammatory process interfere with the patient's daily activity and are frequently associated with disability, depression, and anxiety[1,2].

PASS (Patient's Acceptable Symptoms State) is a single question that measures the value beyond which patients consider themselves well[3]. It is obtained from patients responding YES or NO to a question if their current condition is satisfactory, considering the general functioning and current pain. Additionally, this question reflects patients' perceptions about their disease, including their beliefs, and emotional and cognitive responses that are important to determine their resilience and consequent quality of life[4].

The PASS study is vital in understanding the consequences of the disease from the patients' viewpoint, as doctors and patients may have different perspectives and expectations on good health status[5]. According to Puyraimond-Zemmour et al.[5], when a rheumatic patient judges well-being, he values five areas that can be classified into three categories: physical (pain, function, and sleep), mental (coping), and mixed (that includes fatigue). Generally, clinicians tailor treatment according to objective inflammatory signs of disease activity and such an approach may not be satisfactory as it leaves other health domains uncovered.

Here, a group of Brazilian patients with RA was studied to determine the relationship of their answers to the PASS question with disease activity, pain, functionality, and mood conditions.

METHODS

Ethical issues

This study was approved by the local committee of ethics in research – CAAE-32073120.8.0000.0103 under protocol 4.079.233 from June 9, 2020, and all participants signed consent.

Sample and study design

This is a cross-sectional study with a convenient sample that includes patients with RA from a single rheumatology unit from a university hospital that agreed to participate in the study and came for regular consultation during the 1-year period (July 2020–July 2021). Patients were invited to participate according to appointment order for regular consultations and were included according to willingness to participate in the study. This rheumatology unit belongs to a university hospital that treats patients using public health care in Brazil.

Inclusion and exclusion criteria

To be included, patients should be older than 18 years and fill at least six points on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA[6]. Patients with secondary fibromyalgia, associated inflammatory and neoplastic disorders, and neurological or orthopedical problems that impaired functioning were excluded.

Data collection

Epidemiological (sex, age, age at disease onset, auto-declared ethnic background, and years of formal study), clinical, and serological data were obtained through chart review and direct questioning.

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The disease activity was assessed using SDAI (simple disease activity index) and CDAI (clinical disease activity index); functionality was judged by the HAQ (health assessment questionnaire) and pain through a VAS (visual analog scale; from 0 to 10, where 0=no pain and 10=maximum pain). Anxiety was evaluated using the Beck inventory (p) and depression by the CES-D (Center for Epidemiologic Studies Depression Scale).

The CDAI was measured through a tender and swollen 28-joint count, the patient's global disease activity (from 0–10), and the evaluator's global disease activity (from 0–10). The following cutoff points were used for interpretation: remission ≤2.8, low disease activity >2.8 – ≤10, moderate disease activity >10 – ≤22, and high disease activity >22[7].

The SDAI was measured by the arithmetic sum of tender and swollen 28-joint count, patient's and evaluator's global assessment (from 0–10), and C-reactive protein in mg/dL[7]. Patients with SDAI values ≤3.3 were in remission, with values >3.3 – ≤11 in low disease activity, and values >11 – ≤26 and >26 in high disease activity[7].

The HAQ has questions of about 20 specific activities assessed on a 4-point Likert scale, where 0=without difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The 20 activities are grouped into eight functional categories with each category given a single score equal to the maximum value of its component activities. Thus, the final value ranges from 0=no impairment to 3=maximum impairment[8].

The PASS question was expressed as follows: "Think about all the ways your RA has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable to you?" The YES/NO answer was considered an indicator of satisfaction with the present symptom's state[9].

The CES-D is a 20-item self-report measure that accesses current symptoms of depression on a Likert scale (0=rarely or none of the time; 1=some or little of the time; 2=occasionally or a moderate amount of the time; 3=most or all the time). Values less than 15 are normal, values from 15 to 21 suggest mild to moderate depression, and values over 21 indicate possibility of major depression[10].

The Beck Anxiety Inventory (BAI) is a 21-question multiple-choice self-reported inventory that is used for measuring anxiety severity. Each answer is scored from 0 (not at all) to 3 (severely), and higher total scores indicate more severe anxiety symptoms. The standardized cutoffs are: 0–7=minimal; 8–15=mild; 16–25=moderate; 26–63=severe anxiety[11].

All used instruments were translated and validated into Portuguese[9-11].

Statistical analysis

Data were collected in frequency and contingency tables. Numerical data central tendency were expressed in means and standard deviation (SD) if data were parametric and the medians and interquartile range were nonparametric. Data distribution was judged by the Shapiro-Wilks test. Patients answering YES to PASS were compared with those answering NO using Fisher's and chi-square tests for nominal data and Mann-Whitney and unpaired *t* tests for numerical data. Correlation studies of VAS of pain with depression (CES-D) and anxiety (BAI) were done using the Spearman test. Variables that were associated with the PASS with p>0.1 were studied through multivariate forward logistic regression to evaluate the variable independence, and CDAI, SDAI, HAQ, VAS of pain, CES-D, and BAI were studied as numerical variables. The adopted significance was 5%, and the tests were calculated using the MedCalc Statistical Software v.20.007 (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

Description of the studied sample

In total, 116 patients were included. The sample had a predominancy of middle-aged Caucasian women (Table 1), reflecting the epidemiology of the disease. Median disease activity indexes were compatible with low disease activity, and most patients expressed some degree of anxiety and depression.

In this sample, 34/116 (29.3%) answered NO to the PASS, and 82/116 (70.6%) answered YES.

Comparison of patients with YES and NO responses to Patient's Acceptable Symptoms State

A comparison between the samples with responses YES and NO to PASS is summarized in Table 2.

A logistic regression study using the PASS as a dependent and independent variable: age, SDAI, CDAI, HAQ, VAS of pain, CES-D, and BAI results showed that the only independent variable was depression (p=0.003; OR 1.06; 95%CI 1.02–1.1).

A positive correlation of VAS of pain with CES-D (r=0.29; 95%CI 0.03–0.51; p=0.02) and BAI (r=0.41; 95%CI 0.16–0.60; p=0.001) was found.

DISCUSSION

These results have shown that less than one-third of the patients with RA from this sample (29.3%) were not satisfied with the treatment results. It was also found that patients who answered

Table 1. Epidemiological data, functional and inflammatory indexes, and results of anxiety and depression questionnaires in rheumatoid arthritis patients (n=116).

Female sex/males (n) (%)	99/17	85.3/14.6
Age (years)	30–78	Mean 56.5 (10.4)
Disease duration (years)	1–32	Median 10 (6–17.7)
Auto-declared ethnic background (n)		(%)
Caucasian (n)	109/116	93.9
Afro descendants (n)	5/116	4.3
Asian descendants (n)	2/116	1.7
Positive rheumatoid factor	77/116	66.3
CDAI	0–58	Median 8.5 (2.5–16.4)
SDAI	0–66	Median 10.1 (4.0–21.7)
HAQ	0–2.7	Median 1.0 (0.5–1.7)
Beck Anxiety Inventory (%)	0–52	Median 11 (7–20.0)
No anxiety (n)	34–29.3	
Mild anxiety (n)	39–33.6	
Moderate anxiety (n)	25–21.5	
Severe anxiety (n)	18–15.5	
CES-D	3–55	Median 18.0 (10–26)
Normal (n%)	45–38.7	
Mild to moderate depression (n%)	29–25	
Possibility of major depression (n%)	42–36.2	
VAS of pain	0–10	Median 5.0 (3.0–7.0)

CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; HAQ: Health Assessment Questionnaire; CES-D: Center for Epidemiologic Studies Depression Scale; VAS: visual analog scale; n: number, between brackets; IQR: interquartile range.

NO to PASS had more disease activity, felt more pain, had higher levels of depression and anxiety, and had worse clinical performance than those who answered YES.

The proportion of patients in the PASS in this study was similar to that found in a Swedish sample of patients treated and followed by 5 years, reaching low disease activity (of 22.5%)[2]; it was lower than that found in a Norwegian study that encompassed 1,496 patients (36.8%)[12]. In this study, disease activity, loss of function, pain, anxiety, and depression are associated with this dissatisfaction.

The disease activity has also been linked to PASS in several other studies[2,13]. Cutoff values for composite indices were examined in this context and found compatible with moderate disease activity. Values of DAS-28 <4.21 at week 12 and <3.90 at week 52 in a cohort of patients with RA and established disease were considered acceptable by the patients in the study by Heiberg et al. that analyzed the longitudinal stability of the PASS cutoff points[5]. Another study in patients with early RA followed up for 1 year showed that unsatisfactory PASS outcomes were associated with high or moderate disease activity since the patients also had associated high PROM (patient-reported outcome measures) scores[13]. Eberhard et al.[2] further explored this aspect and found that patients with "unacceptable pain" had low swollen joint counts and a high VAS for pain. Discrepancies between the evaluation of inflammatory disease activity and patient's expectations have been reported earlier by others[14,15], highlighting the greater importance of symptoms over inflammatory findings in this setting. Thus, although important, the inflammatory component of the disease may not be the main determinant of PASS.

Arthritis pain is, at least partially, secondary to the action of pro-inflammatory cytokines, which activate nociceptors in

Table 2. Comparison of rheumatoid arthritis patients with answers YES and NO to PASS (Patient's Acceptable Symptoms State).

	PASS: Yes n=82 (%)	PASS: No n=34 (%)	p-value
Female sex (n)	68–82.9	31–91.1	0.38
Age – mean (SD) (years)	57.6 (10.3)	53.9 (10.5)	0.08
Disease duration – median (IQR)	10.0 (6.0–18.0)	12.5 (7.7–17.2)	0.37
Positive rheumatoid factor (n)	55/80–68.7	22/33–66.6	0.82
SDAI – median (IQR)	8.8 (2.8–19.0)	16.15 (6.0–25.6)	0.08
CDAI – median (IQR)	14.0 (5.5–21.5)	8.0 (2.0–15.0)	0.03
HAQ – median (IQR)	0.87 (0.2–1.4)	1.37 (0.9–2.1)	0.001
Beck Anxiety Inventory – median (IQR)	11.0 (6.0–17.0)	13.5 (7.0–25.5)	0.05
VAS pain – median (IQR)	5.0 (2.7–6.2)	6.0 (3.7–7.2)	0.03
CES-D – median (IQR)	17.0 (9.0–22.0)	22.5 (16.2–34.5)	0.001

PASS: Patient's Acceptable Symptoms State; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; HAQ: Health Assessment Questionnaire; CES-D: Center for Epidemiologic Studies Depression Scale; VAS: Visual analogic scale; n: number; SD: standard deviation; IQR: interquartile range.

the synovium[16]. However, it has been documented that a significant group of patients with RA continues experiencing pain despite good inflammatory control of their disease due to neuropathic mechanisms secondary to central sensitization[2,17]. Consequently, directing the RA treatment according to the measurement of objective outcomes may not be enough to achieve good results from the patient's viewpoint. A central sensitization pain treatment requires treating neural pain with drugs, such as gabapentin, or antidepressive agents, such as duloxetine or imipramine, and may benefit from a multidisciplinary team management[18]. In this context, McWilliams et al.[19] observed the importance of early intervention in pain treatment, as patients with high pain levels in the beginning of the disease have an increased risk of long-lasting pain. Considering these, the study on the impact of mood disorders may be important and is poorly explored in the PASS setting. Depression was associated independently with PASS in this study. Moreover, at present, the pain scale is correlated with depression and anxiety, as already observed by others[20]. A systematic review of osteoarthritis pain showed that pain severity was correlated with emotional impairment (anxiety/depression) severity in these patients[20]. Although depression and pain may have common physiopathological links, both have a biochemical basis, focusing on the serotonergic and norepinephrine system and suffers modulation by the same brain structures, that is, the prefrontal cortex[20,21]. Furthermore, mood disorders interfere with pain acceptance, an important mechanism for coping with pain and channeling patients' thoughts and sensations toward valuable goals and purposes[22]. Pain is also considered to predict the level of fatigue and work disability[23], amplifying patients' dissatisfaction.

Epidemiological variables have been studied in the PASS. Also, Salaffi et al.[24] found that patients in the PASS were older, similar to what has been observed in spondyloarthritis[25]. Additionally, Duarte et al. observed that being older than 50 years was associated with PASS in RA[26]. Therefore, the patients in the PASS in this study were older than those not in the PASS, although this difference was not statistically significant.

This study is limited by the small number of participants and its cross-sectional design. In addition, socioeconomic factors and drugs used for the RA treatment were not studied and could have had some influence on the patient's well-being. Nevertheless, all study patients were from a public health-care center that attends to individuals with low socioeconomic status, and this could have given some homogeneity in this context between those answering YES and NO to the PASS. Its main value is that, in this sample, depression was an independent variable in the patient's acceptance of the disease. Clinicians caring for RA patients should be alert for depression signs, introducing early treatment in order to improve their quality of life.

In conclusion, disease activity, loss of function, pain, anxiety, and depression were linked to answering NO to the PASS question. Finally, depression was the only independent variable.

AUTHORS' CONTRIBUTION

PHS: Conceptualization, Writing – original draft. **MHJ:** Conceptualization, Writing – original draft. **BK:** Conceptualization, Writing – original draft. **RN:** Conceptualization, Data curation, Formal Analysis, Writing – original draft. **TS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft.

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