Attainment of the Patient-acceptable Symptom State in 548 Patients with Rheumatoid Arthritis: Influence of Demographic Factors

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Short Title: PASS and socio-demographic factors

ABSTRACT

Objectives: To explore the clinical and socio-demographic factors associated with Patient Acceptable Symptom Status (PASS) in Rheumatoid Arthritis (RA).

Methods: In a post-hoc analyses of a cross-sectional study, RA patients from 11 countries were included. PASS was assessed as acceptable/not acceptable status by the patient. Variables collected included socio-economic (gender, age and country gross domestic product (GDP) per capita) and clinical variables: DAS28-3vESR (28 joint counts and Erythrocyte Sedimentation Rate), the patient-reported Rheumatoid Arthritis Impact of Disease (RAID) score and its seven domains (scored 0 to 10). Patients in PASS or not were compared through univariable tests and factors associated with PASS assessed by multivariable forward conditional logistic regression. A similar analysis was performed in the subgroup patients in DAS28 remission (n=168).

Results: A total of 548 patients were included:80.5% female, mean (±SD) age 55.8±12.8 years, disease duration 13.6±10.6 years, DAS28 3.6±1.5. Overall, 360 (65.7%) considered themselves to be in PASS. Independent factors positively associated with being in PASS were age>50 years (odds ratio, OR 1.67; [95% confidence Interval:1.04-2.67]), a lower DAS28 (OR:1.28 [1.08-1.52]), lower pain (OR:1.45 [1.27-1.64]) and better emotional well-being (OR:1.28 [1.13-1.45]). Among patients in remission, being in PASS was positively associated with less severe pain (OR:2.50 [1.79-3.84]), age>50 years (OR 3.30 [1.03 to10.87]) and living in a country of the low GDP category (OR:5.08; [1.34-19.23]).

Conclusions: Being in PASS is related to many factors besides disease activity, including age, perceived impact of the disease and national GDP.

KEYWORDS: Rheumatoid Arthritis, Patient Reported Outcomes, Patient Acceptable Symptom State, Disease Activity, Socio-Demographic Aspects

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1. INTRODUCTION

In a patient-centred care perspective, patients´ satisfaction with their health condition becomes one of the most relevant objectives of medical practice, in parallel with physician-centred targets. Therefore, the evaluation of individual patient perceptions of disease impact, through Patient Reported Outcomes (PROs) should be encouraged, in addition to disease activity scores.

Patient Acceptable Symptom State (PASS) is a strictly patient-centred outcome that merits consideration as a treatment target [1]. It is assessed through a dichotomized simple question about patient's global satisfaction with their current symptom status and is recognized as facilitating the communication and decision sharing between patients and health-care providers [1-3].

Understanding the factors associated with PASS is helpful to understand the underlying message and to define the most adequate management strategy, particularly in case of discordance between the perceptions of patient and the physician [4]. A patient considers himself as being in an acceptable status, despite active arthritis, probably needs careful explanations to ensure adherence to additional treatment. Conversely, in patients in inflammatory remission who continue to experience a non-satisfactory status, underlying reasons should be evaluated and addressed through adjunctive interventions, without intensification of immunosuppressive therapy.

Previous studies have shown that PASS is related with disease activity, and with the patient´s perception of impact, with pain, function and physical well-being representing the most influential factors [5-7]. However, the role of non-disease-related factors, which have been evaluated in different rheumatic conditions [3, 8-10], remains unclear in RA. The effect of gender and age on acceptable status remains controversial [3, 6, 9-11]. Substantial differences in PASS thresholds have been reported between English-speaking versus non–English-speaking countries, regarding spondylarthritis [3]. However, these findings were not confirmed in other studies addressing different rheumatic conditions[12]. Moreover, the effect of the country´s socio-economic welfare in terms of gross domestic product (GDP) per capita has not been evaluated.

This study aimed at addressing these knowledge gaps by evaluating the socio-demographic factors associated with PASS in RA in a multinational cohort of patients.

2. MATERIAL AND METHODS

2.1 Study design and patients:

This was a cross-sectional analysis of data from the RAID (RA Impact of Disease) study, an international multicentric study performed in 2008-2009 involving adult RA patients from 10 European countries [13], with additional data from a Portuguese single centre (2017-2018), a country not included in the RAID Study. All patients were adults with the diagnosis of RA [14], able to fill in the questionnaires and willing to provide informed consent. This study was conducted under approval of ethics committees from the participating countries.

The present analysis only included patients without missing data regarding PASS, DAS28-3vESR and individual items of the RAID questionnaire.

2.2 Outcome of Interest

PASS was assessed in a binary way (PASS yes/no) through the question: "*Think about all the ways your RA has affected you during the last week. If you were to remain for the next few months as you were during the last week, would this be: a) Acceptable or b) Unacceptable*". [7, 12]

2.3 Data Collection

Socio-demographic data (age, gender and country) were collected. Information on GDP *per capita* (adjusted for purchasing power parity, measured in international dollars) for each country was extracted from the reports of the International Monetary Fund for 2009 (for countries of RAID study) and for 2018 for Portugal [15]. GDP was dichotomised in low-GDP and high-GDP countries, with a cut-off at 35000 international dollars per capita, which was the threshold that discriminated best between groups after visual data inspection.

RA-related clinical characteristics were recorded, including tender 28-joint count (TJC), swollen 28-joint count (SJC) and Erythrocyte Sedimentation Rate (ESR). Disease activity was assessed using the 28-joint disease activity score (DAS28), calculated based on TJC, SJC and ESR (3v). In the absence of validated cut-offs for DAS28-3vESR, those validated for DAS28-4vESR were considered. Disease activity was, thus, categorized as: *High disease activity >5.1; Moderate* Disease Activity [3.2 to 5.1]; Low disease activity [2.6 to 3.2[and Remission <2.6 [16]. The impact of RA was assessed using the RAID score. This is a composite measure specific for RA that reflects the

patient´s perception of the impact of disease on seven domains of health (pain, fatigue, physical function, sleep disturbance, emotional well-being, physical well-being and coping) [13]. Each domain is assessed through a single question answered on a 0 (the best state) to 10 (the worst sate) numerical rating scale. Scores of the individual domains were collected and the global RAID score was computed according to the validated algorithm [13].

2.4 Statistical Methods

Descriptive characteristics are presented as mean and standard deviation (±SD) for continuous variables and as proportions (%) for categorical variables.

Differences in variables between patients in PASS and non-PASS were tested using the t-test for independent samples or Chi-square test, as adequate. Variables with $p<0.1$ in univariate analysis, gender, age and GDP category were included in stepwise multivariate logistic regression (Forward Conditional analysis), with PASS as dependent variable. This analysis was repeated in the subgroup of patients in inflammatory remission, in order to explore factors independent of inflammation and understand the reason of non-PASS in patients who have achieved the inflammatory remission target.

Statistical Analysis was performed using the SPSS® software, version 24. Statistically significant effects were assumed for $p<0.05$.

2.5 Ethics

The RAID Study was conducted with approval of the ethics committees in the participating countries. Portuguese study was approved by the Ethics Committee of the Centro Hospitalar Universitário de Coimbra (CHUC-160-17). All patients signed a written informed consent before to participate.

3. RESULTS

3.1 Demographic and clinical characteristics

In total, 548 patients from 11 countries (number per country ranging from 34 (Greece to 96 (Portugal)) were included (supplementary table 1). Their demographic and clinical

characteristics are presented in table 1. The majority were women (80.5%), with a mean age of 55.8±13.0 years, and a mean disease duration of 13.6 ±10.5 years.

Disease activity, as measured by DAS28-3vESR, was reflected by a mean score of 3.6 ±1.5 with 44.2% of patients being in remission or low disease activity. Impact of disease assessed through RAID score was moderate to high (mean 4.2±2.2), with pain (mean 4.6±2.6), fatigue (mean 4.5±2.7) and function (mean 4.4±2.6) being the most severely affected domains.

3.2 Prevalence and correlates of PASS status

Of 548 patients, 360 (65.7%) rated their symptom status as acceptable. Disease activity (DAS 28 mean 3.1±1.3 vs 4.4±1.5), p<0.01), global impact (mean global RAID score 3.3±1.8 vs 5.8±1.8, p<0.01) as well as in each of the seven domains of RAID were significantly lower in patients in PASS status (p<0.001). (Table1) Overall, the group of patients in PASS had a higher proportion of people aged > 50 years (72.5% vs 68.3%, p=0.019). No differences were observed in regarding gender, GDP category or disease duration.

In multivariable regression analysis, lower disease activity by DAS28-3vESR (OR=1.28, 95%CI: 1.07 to 1.52), less intense pain (OR=1.45, 95%CI:1.27 to 1.65), better emotional well-being (OR=1.28, 95%CI:1.19 to 1.45), and age>50 years (OR=1.67, 95%CI:1.04 to 2.67) were associated with being in PASS. (Table 2)

3.3 Subgroup analysis of patients in inflammatory remission

Considering only patients in inflammatory remission (n=168) according to DAS28-3vESR, living in a low GDP country (61.1% vs 54.2%) and being older than 50 years (75.7% vs 50.0%) were associated with higher odds of being in PASS. Despite all being in remission, patients in non-PASS still perceived higher impact in all domains than patients in PASS (p<0.01), scoring ≥5 in all domains of RAID, except for coping (mean 3.9±2.7) and for sleep disturbance (mean 4.5±3.2). Independent factors associated with being in PASS status were lower levels of pain (OR=2.50, 95%CI=1.79 to 3.84), living in a country with a GDP/capita <35000 international dollars (OR=5.08, 95%CI=1.34 to 19.23) and age >50 years (OR=3.30, 95%CI=1.03 to 10.87). (Table 2)

4. DISCUSSION

This report shows that factors not related to the disease, such as age and GDP/capita, have an important influence on PASS status of patients with RA, which is particularly relevant in patients in inflammatory remission.

Two-thirds of all included patients were in PASS status. Coherently, patients who considered themselves to be in a non-acceptable status reported worse scores for all domains of health and had higher levels of disease activity. Among the factors related to the disease, pain was the most important factor preventing patients from reaching an acceptable status, which is in agreement with previous studies [5, 6, 17]. As expected, and similarly to other studies, disease activity was independently associated with being PASS. Emotional well-being had a significant impact on PASS status in our study, similarly to other study where depression was independently associated with being in PASS.[17] Physical well-being, fatigue, function, sleep and coping were not associated with PASS/non-PASS in multivariable analysis in our study. Interestingly, older age, in and of itself, was the strongest predictor of PASS status in multivariable analysis, i.e, after correction or potential confounders.

Among patients in inflammatory remission, 15% still considered their status as non-acceptable. These findings are aligned with observations that remission of inflammation does not always result in symptom remission, [18] thus suggesting that other factors besides disease activity need to be taken into consideration. Understand the reasons underlying a non-acceptable status is particularly relevant in this subgroup of patients to guide adjuvant interventions, as disease activity is already under control. Our analyses indicate that that GDP/capita is the strongest independent factor of PASS status, in these patients, followed by pain and age. Similar observations regarding age have been previously reported in SpA [3] and osteoarthritis [10], but not consistently in RA [6] [7, 17, 19], with only one study showing that older age was independently associated with being in PASS.[17] Similar correlates of GDP have been reported regarding other PROs, such as PGA and fatigue [20, 21]. It is conceivable that higher expectations associated with higher GDP and younger age play a role in the observed associations. Naturally, factors associated with ethnical and cultural backgrounds may also play a role, independently of the economy, as they have been shown to influence the self-perceived impact of RA in several domains or ability to cope with disease [22] as well with of anti-rheumatic drugs persistence in RA.[23] These could not be addressed in the present study.

Our study has some limitations. The cross-sectional design allowed assessment of patient's satisfaction in one single visit. However, patient satisfaction can be affected by previous experiences and vary according to whether there has been an improvement or worsening of health compared to the past [6]. The patients included in this analysis were enrolled in different decades, and significant development in RA treatment occurred during this period of time, which can be considered a limitation of our study. Education level, which was associated with other RA outcomes in previous studies was not considered in our study. However, PASS wasn´t associated with education level in the recent study. [19] Despite the large sample size, the number of patients per country is small and the influence of GDP should be interpreted with caution and deserve confirmation in future studies including larger samples from the different countries. Cultural and behavioural factors, strongly dependent of the country residence and of the country of birth, were not considered in this study. However, GDP could be a surrogate marker for other objective and cultural factors.

In conclusion, reaching remission doesn´t equate to being in a PASS status and socio-demographic characteristics, including as age or country of residence can have a relevant role in patients´ perception of an (un)acceptable state. Dedicated research is warranted to understand the factors that drive patients' unsatisfaction with their health despite inflammatory remission and to design appropriate holistic interventions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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Table 1: Socio-demographic and clinical characteristics of 548 patients with RA patients, according to PASS status.

	All (n=548)	PASS (n= 360)	No PASS (n=188)	p-value
Female N (%)	441 (80.5)	283 (78.6)	158 (84.0)	0.13*
Age (mean /SD)	55.8 (13.0)	56.5 (13.3)	54.4 (12.2)	0.06*
Age >50 Yrs N (%)	379 (69.2)	261 (72.5)	118 (62.8)	0.02#
GDP Low GPD N (%)	318 (58.0)	204 (56.7)	114 (60.6)	0.37#
DAS28-3vESR	3.6 (1.5)	3.1 (1.3)	4.4 (1.5)	<0.01*
Remission N (%)	168 (30.7)	144 (40.0)	24 (12.8)	n.a
Low N (%)	74 (13.5)	60 (16.7)	14 (7.4)	n.a
Moderate N (%)	208 (38.0)	129 (35.8)	79 (42.9)	n.a
High N (%)	98 (17.9)	27 (7.5)	71 (37.8)	n.a
RAID Score ((0 to 10))	4.2 (2.2)	3.3 (1.8)	5.8 (1.8)	<0.01*
RAID Pain (0 to 10)	4.6 (2.6)	3.6 (2.2)	6.5 (2.3)	<0.01*
RAID Function (0 to 10)	4.4 (2.6)	3.4 (2.2)	6.2 (2.3)	<0.01*
RAID Fatigue (0 to 10)	4.5 (2.7)	3.7 (2.5)	6.0 (2.3)	<0.01*
RAID Sleep (0 to 10)	3.6 (2.8)	3.0 (2.6)	4.7 (2.9)	<0.01*
RAID Emotional Well-being (0 to 10)	4.2 (2.5)	3.3 (2.1)	5.9 (2.2)	<0.01*
RAID Physical Well-being (0 to 10)	3.9 (2.5)	3.1 (2.3)	5.3 (2.4)	<0.01*
RAID Coping (0 to 10)	3.7 (2.5)	3.0 (2.2)	5.2 (2.3)	<0.01*

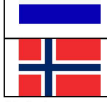
Values are the mean ± SD unless indicated otherwise. PASS: Patient Acceptable Symptom State; Yo: years old; GDP: Gross Domestic Product; DAS 28-ESR: Disease Activity Score, Erythrocyte Sedimentation Rate; RAID: Rheumatoid Arthritis Impact of Disease. *Independent Samples T-Test, # Chi-2 Test. n.a: not analysed

Table 2: Adjusted Odds Ratio (OR) for being in PASS for all patients and for patients in disease remission

All Patients (n=548)		
	OR	**95%CI**
Age (>50 vs ≤50 years)	1.67	1.04-2.67
Pain (0-10, per reduction of 1 point)	1.45	1.27-1.64
RAID emotional Well-being (per reduction of 1 point)	1.28	1.13-1.45
DAS28-3vESR (per reduction of 1 point)	1.28	1.08-1.52
Patients in disease Remission (n=168)		
	OR	**95%CI**
Age (>50 vs ≤50 years)	3.30	1.03-10.87
GDP per capita of country (Lower vs Higher)	5.08	1.34-19.23
Pain (0-10, per reduction of 1 point)	2.50	1.79-3.84

GDP: Gross Domestic Product; OR: Odds Ratio; CI: confidence interval

Supplementary table 1: Clinical Characterization per country

	Country (n)	GDPpercapita, 1000 international dollars**	DAS28-3vESR*	Remission (%)	PASS Total (%)	PASS in Remission (%)
	Turkey (34)	15.64	4.1±1.6	23.5	64.7	75.0
	Romenia (51)	16.40	5.0±1.2	3.9	47.1	100.0
	Estonia (51)	20.97	3.8±1.4	19.6	52.9	70.0
	Greece (39)	30.35	4.3±1.2	7.7	43.6	100.0
	Spain (47)	32.00	3.5 ±1.4	34.0	72.3	100.0
	Portugal (96)	32.01	2.3±1.1	65.6	80.0	85.7
	France (42)	36.26	3.7±1.3	21.4	59.5	66.7
	Finland (48)	37.35	2.7±0.9	54.2	70.8	76.9
	Germany (50)	38.74	4.2±1.4	12.0	58.0	83.3
	TheNetherlands (45)	44.51	2.6±1.2	51.1	91.1	95.7
	Norway (45)	61.28	4.3±1.2	6.7	60.0	100.0

*Values are the mean ± SD. PASS: Patient Acceptable Symptom State; GDP: Gross Domestic Product; DAS28-3vESR: Disease Activity Score 3 variables, Erythrocyte Sedimentation Rate, Countries are ordered by increasing GDP (international dollars). **International dollars are purchasing power parity adjusted dollars, 2009 (all, except for Portugal) and 2018 (Portugal)