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Article

Impact and Prevalence of Depression and Anxiety in Rheumatoid Arthritis – a Cross-Sectional Study with Self-Reported Questionnaires

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Abstract: Objective: The study aims to screen for depression and anxiety a real-life sample of RA patients and to observe whether RA phenotype characteristics and RA disease activity measures are associated with depression and anxiety. **Methods:** This cross-sectional study screened for depression and anxiety using the PHQ9 and HADS, self-reported questionnaires, all patients with diagnosed RA that came for their disease follow-up during one month. The follow-up captured the date of RA diagnosis, pharmacological treatment, clinical examination, blood sampling, functional and radiographic assessment. The cut-off for positive screening of depression was a PHQ9 of 10 or more and a HADS-D of over 10, and the positive cut-off for anxiety was a HADS-A of over 10. **Results:** According to the medical history the prevalence of depression and anxiety in the 209 patients included was 10%, respectively 8.1%, while the likely depression diagnosis according to PHQ was 34.4% and according to HADS-D was 14.8% and a likely anxiety diagnosis using the HADS-A was 32.5%. The subgroup of patients that positively screened for depression using the self-reported questionnaires PHQ9 and HADS-D had significantly higher DAS28, disease activity class, tender joint count, VAS, functional stage, with some particularities regarding ESR and radiographic stage which were higher just in the HADS-D of more than 10 subgroup and glucocorticoid use which was higher just in the PHQ over 10 subgroup. Regarding patients with a HADS-A of more than 10 they were more frequently women, and had higher tender joint count and functional stage. **Conclusions:** Depression and anxiety are highly prevalent and underdiagnosed in the RA population and are associated with higher levels of pain, physical disability and disease activity.

Keywords: rheumatoid arthritis; depression; anxiety; disease activity; quality of life

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that involves the synovial joints, where it determines a chronic inflammatory process that leads to early, progressive and irreversible osteoarticular damage. RA is frequently associated with various extraarticular manifestations, which through different complications reduce life expectancy by 5 to 10 years. The prevalence of RA in the general population is 0.5-1%, making it the most frequent rheumatic inflammatory disease, representing a major public health problem [1]. One of the most frequently associated comorbidities in RA is depression, with a prevalence of 15% according to a paper published by Dougados *et al.* in 2014 [2]. The prevalence of depression has been shown to be 2–3 times higher than in the general population, with a meta-analysis done by Matcham *et al.* in 2013 reporting that 16.8% of RA patients have a major depressive disorder [3]. In different studies there is a high variability for depression prevalence in RA, ranging from 2% in Morocco to 33% in the USA, probably caused by the differences in study design, the variations in the definitions of depression and the methods used for measuring depressive symptoms [4]. In the general population, depression has a prevalence of 6% [5]. Another frequent comorbidity in RA is anxiety with 25.1% of patients

screening positive according to the Generalised Anxiety Disorder questionnaire [6,7], while in the general population the prevalence is 4.03% [8]. Both depression and anxiety are screened positive in 16.3% of RA patients [7].

RA patients with associated depression have a poor long-term outcome, they suffer from higher levels of pain, fatigue, disease activity and physical disability. Depression lowers treatment adherence, causing more comorbidities, and leading to higher mortality rates, partly through increased suicide risk. Health service utilization and healthcare costs are increased in this patients directly through hospitalization, but also indirectly through loss of work productivity. Ultimately RA patients with depression tend to have a lower quality of life, a fact that is reflected in all the domains of the Quality of Life questionnaire [9,10].

Associated anxiety worsens several outcomes in RA patients, leading to poor long-term outcome, by increasing morbidity, mortality and pain [11]. It alters sleep patterns, leading to sleep disorders such as early awakening and insomnia. Similarly to depression, anxiety lowers patients' adherence to treatment and it leads to high medical costs through high utilization of health resources [12] and it increases sick leaves affecting work productivity [13]. The multiple effects of anxiety on RA patients finally contribute to a decline in their quality of life [14].

The psychiatric interview and diagnosis according to Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) criteria are the gold standard for diagnosing depression and anxiety [15], but they are expensive and time consuming, making them difficult to use in a busy hospital setting. In research studies on the prevalence of depression or anxiety in RA, self-reported screening questionnaires are used, because they require less funds and are faster. This may lead to overestimation of prevalence, as screening tools tend to prioritize sensitivity over specificity [16].

In 2013 a meta-analysis done by Matcham *et al.* on depression definitions in RA patients showed that some of the screening tools used to detect depression are Patient Health Questionnaire-9 (PHQ-9), Hospital Anxiety and Depression Scale (HADS), Inventory to Diagnose Depression (IDD), Center for Epidemiological Studies Depression Scale (CESD), Beck Depression Inventory (BDI), and the Geriatric Depression Scale (GDS), the most frequently used being the HADS and the CESD. Also HADS was the most frequently used tool to identify anxiety. The definition of depression and anxiety based on these questionnaires included possible or probable positive diagnosis by using either one or multiple thresholds [3].

Self-reported questionnaires are not completely accurate, but they are useful tools for screening depression and anxiety in RA patients who need further psychiatric evaluation. Screening for mental illness is extremely important, because the growing evidence suggests clearly that detecting and correctly treating depression and anxiety in RA patients leads to a better quality of life, by improving pain, fatigue, physical disability and lowering RA disease activity. In this context, the study aims to screen for depression and anxiety a real-life sample of RA patients and to observe whether RA phenotype characteristics and disease activity measures like Disease Activity Score 28 (DAS28) and its components are associated with depression and anxiety.

2. Materials and Methods

2.1. Patients

The study screened all patients diagnosed with RA according to their attending physicians who randomly came for follow-up evaluations in the "Dr. Ion Stoia" Clinical Center of Rheumatic Diseases from Bucharest between September and November 2024. Additional inclusion criteria were: fulfillment of the 2010 American College of Rheumatology – European League against Rheumatism classification criteria for RA [17], and age above 18 years. Exclusion criteria were: overlapping chronic autoimmune or inflammatory conditions, a current/recent diagnosis of cancer, other psychiatric disorders (schizophrenia, bipolar disorder, psychosis), experimental RA treatments, substance use disorders, cognitive impairment, pregnancy, recent major life events (trauma, bereavement).

Preexisting depression and anxiety were defined as either patient-reported medical history or if the patients were taking specific psychiatric medication for anxiety or antidepressants (namely tricyclic antidepressants, atypical antidepressants, selective serotonin re-uptake inhibitors, selective serotonin and norepinephrine re-uptake inhibitors, norepinephrine and dopamine reuptake inhibitors, noradrenaline and specific serotonergic antidepressants, serotonin modulator and stimulator, serotonin antagonist and reuptake inhibitor or monoamine oxidase inhibitors, all prescribed by their treating psychiatrists). All patients gave written informed consent and the study was approved by the hospital's ethics committee. Each patient underwent in the same day all study procedures (clinical interview, clinical examination, peripheral venous blood sampling for laboratory tests, hand and feet X-rays, and questionnaire answering).

2.2. RA Evaluation

Clinical interviews and/or medical records allowed to capture the date of RA diagnosis (used to calculate RA disease durations) and current pharmacological treatment (biologic, conventional synthetic or targeted synthetic disease-modifying antirheumatic drugs - b/cs/tsDMARDs and glucocorticoids). Laboratory tests included autoantibodies (rheumatoid factor – RF and anti-citrullinated protein antibodies – ACPA, if not tested within the last year) and acute phase reactants (C-reactive protein – CRP, normal below 5 mg/L; erythrocyte sedimentation rate – ESR, normal below 20 mm/h), all done by the local laboratory using commercially available kits. Each attending rheumatologist prompted the patients to report a global health evaluation (on a 100 mm visual analogue scale - VAS), evaluated disease activity by counting the numbers of tender (TJC28) and swollen joints (SJC28) and classified the patient functionally, using Steinbrocker functional capacity classes [18]. Disease activity classes were defined with DAS28 [19,20], which was calculated with 4 variables with CRP, as follows: remission ($\text{DAS28} < 2.6$), low ($2.6 \leq \text{DAS28} \leq 3.2$), moderate ($3.2 < \text{DAS28} \leq 5.1$) and high disease activity ($\text{DAS28} > 5.1$). All radiographic progression staging was labeled using Steinbrocker criteria by the clinic's imaging expert [18].

2.3. Depression Questionnaires

Each patient filled in without external aid two questionnaires: PHQ-9 [21] and HADS [22]. PHQ9 is a widely used, validated tool for screening, diagnosing, monitoring, and measuring the severity of depression. It consists of 9 items, each corresponding to the diagnostic criteria for major depressive disorder. Questions assess symptoms like mood, sleep, energy, appetite, and suicidal thoughts over the past two weeks. Each item is scored on a scale from 0 (not at all) to 3 (nearly every day), with a total score range of 0–27, with the following categories: minimal depression (PHQ9 = 0–4), mild depression (PHQ9 = 5–9), moderate depression (PHQ9 = 10–14), moderately severe depression (PHQ9 = 15–19) and severe depression (PHQ9 = 20–27). HADS is a validated self-report questionnaire used to assess symptoms of anxiety and depression, which allows for the exclusion of somatic symptoms to avoid confounding with physical illness, making it particularly useful in hospital or outpatient settings. It contains 14 items divided into two subscales for anxiety (HADS-A, 7 items) and depression (HADS-D, 7 items). Each item is scored from 0 to 3, with subscale scores ranging from 0–21. The global score indicate severity: normal (HADS = 0–7), borderline abnormal (HADS = 8–10) and abnormal (HADS = 11–21, clinical level).

2.4. Statistics

The normality of data distribution was assessed using descriptive statistics, normality, stem plots and leaves, and Kolmogorov-Smirnov tests corrected by Lilliefors. Continuous variables are reported as mean (standard deviation) if normally distributed, or as median (interquartile range) if non-normally distributed, while dichotomous variables are reported as percentage of group or subgroup. Independent 2-sided t tests or Mann-Whitney U or Kruskal Wallis tests were used to evaluate differences in continuous variables between subgroups of categorical variables, while

associations between categorical variables were studied using χ^2 tests. Statistical tests were considered significant if $p < 0.035$ for an alpha level of 0.05 and Bonferroni correction in order to avoid the type I error. Statistical analysis was performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp., Armonk, New York, USA).

3. Results

The study included 209 patients, of which 92.3% were women, with an average age of 62.1 (11.5) years (Table 1). Most patients had established disease, with a predominance of positive RF and ACPA, and significant structural damage and functional disability. As a group, approximately half were within DAS28-defined treatment target of remission or low disease activity. Almost all patients were on csDMARDs, 41.6% had a b/tsDMARDs and 34.9% were on oral glucocorticoids at the time of the study.

Medical history revealed a significant proportion of patients with known depression (10.0%) and anxiety (8.1%), and only 7.7% of patients were receiving prescribed antidepressants. Likely depression diagnoses were screened for 34.4% who had a PHQ9 of 10 or more, and respectively for 14.8% of patients who had a HADS-D of more than 10 (Table 2). Also, likely anxiety diagnoses were screened for 32.5% who had a HADS-A of more than 10 (Table 2). Compared to patients with a PHQ9 score of below 10, those with a PHQ9 score of 10 or more presented significantly higher numbers of tender and swollen joints, global patient evaluations, DAS28, glucocorticoid treatment frequency, functional stages and disease activity classes (Table 3). Similarly, compared to patients with a HADS-D score of 10 or below, those with a HADS-D score of more than 10 presented significantly higher mean disease duration, ESR levels, numbers of tender and swollen joints, global patient evaluations, DAS28, radiographic and functional stages and disease activity classes (Table 4). Compared with patients scoring 10 or bellow on the HADS-A, those with questionnaire-defined anxiety were more frequently women and they had significantly higher functional staging of RA and higher tender joint counts (Table 5).

PHQ9 and HADS-A scores were significantly higher in women and in patients with more severe joint damage, functional stage and disease activity class (Table 6). Additionally, HADS-D scores were significantly higher in the same patients and in those with glucocorticoid use.

Table 1. General characteristics of RA patients (n = 209).

women	92.3%	CRP (mg/L)	4.7 (9.3)
age (y)	62.1 (11.5)	ESR (mm/h)	28.5 (20.1)
RA duration (y)	11.1 (9.9)	TJC28	3 (5)
RF positive	70.3%	SJC28	1 (3)
ACPA positive	75.6%	PtGA (mm)	42 (25)
RF and ACPA positive	64.6%	DAS28*	3.5 (1.5)
SRPC1	24.4%	DAS28 remission	30.1%
SRPC2	44.0%	DAS28 LDA	17.7%
SRPC3	18.2%	DAS28 MDA	34.4%
SRPC4	13.4%	DAS28 HDA	17.7%
SFCC1	21.5%	≥ 1 csDMARDs	90.9%
SFCC2	58.4%	b/tsDMARD	41.6%
SFCC3	19.1%	glucocorticoids	34.9%
SFCC4	1.0%		

Notes: * DAS28 is calculated with 4 variables and CRP. Age, disease duration, ESR, PtGA, DAS28 are reported as mean (SD), while CRP, TJC, SJC are reported as median (IQR). Nominal variables are reported as percentage of subgroup. Normal ranges: CRP < 5 mg/L; ESR < 20 mm/h. Abbreviations: ACPA – anti-citrullinated protein antibodies; b/cs/tsDMARDs – biologic, conventional synthetic or targeted synthetic disease-modifying antirheumatic drugs; CRP – C-reactive protein; DAS28 – disease activity score

with 28 joints; ESR – erythrocyte sedimentation rate; HDA – high disease activity; IQR – interquartile range; LDA – low disease activity; MDA – moderate disease activity; PtGA – patient global assessment; RA – rheumatoid arthritis; RF – rheumatoid factor; SD – standard deviation; SFCC – Steinbrocker functional capacity class; SJC – swollen joint count; SRPC – Steinbrocker radiographic progression class; TJC – tender joint count; y – years.

Table 2. Depression and anxiety characteristics (n = 209).

depression history	10.0%	HADS-D	6.3 (4.0)
anxiety history	8.1%	HADS-D > 10	14.8%
antidepressants	7.7%	HADS-D normal	64.6%
PHQ9	8.1 (4.9)	HADS-D borderline	21.1%
PHQ9 ≥ 10	34.4%	HADS-D abnormal	14.4%
PHQ9-DS: none/minimal	27.3%	HADS-A	8.6 (4.4)
PHQ9-DS: mild	38.3%	HADS-A > 10	32.5%
PHQ9-DS: moderate	25.4%	HADS-A normal	40.2%
PHQ9-DS: moderate-severe	8.1%	HADS-A borderline	26.8%
PHQ9-DS: severe	0.5%	HADS-A abnormal	33.0%

Notes: PHQ9 and HADS-D/A are reported as mean (SD). Abbreviations: DS – depression severity; HADS D/A - Hospital Anxiety and Depression Scale Depression/Anxiety; PHQ-9 – Patient Health Questionnaire-9; RA – rheumatoid arthritis; SD – standard deviation.

Table 3. Comparison of RA variables according to PHQ9 cutoff.

	<i>PHQ9</i> <10 (<i>n</i> = 137)	<i>PHQ9</i> ≥10 (<i>n</i> = 72)	<i>p</i>		<i>PHQ9</i> <10 (<i>n</i> = 137)	<i>PHQ9</i> ≥10 (<i>n</i> = 72)	<i>p</i>
women	90.5%	95.8%	0.169	CRP (mg/L)	4.4 (8.1)	6.2 (14.1)	0.094
age (y)	61.5 (11.8)	61.9 (11.0)	0.646	ESR (mm/h)	26.3 (18.9)	31.9 (20.5)	0.112
RA duration (y)	10.5 (8.9)	11.5 (10.4)	0.418	TJC	2 (6)	4 (7)	0.000
RF +	71.3%	70.4%	0.892	SJC	0 (3)	2 (4)	0.006
ACPA +	75.0%	78.9%	0.534	PtGA (mm)	36 (24)	54 (24)	0.000
RF, ACPA +	62.8%	68.1%	0.448	DAS28*	3.2 (1.4)	4.1 (1.4)	0.000
SRPC			0.106	DAS28 activity			0.000
SRPC1	29.2%	15.3%		remission	38.7%	13.9%	
SRPC2	41.6%	48.6%		LDA	16.1%	20.8%	
SRPC3	15.3%	23.6%		MDA	34.3%	34.7%	
SRPC4	13.9%	12.5%		HDA	10.9%	30.6%	
SFCC			0.014	≥ 1 csDMARDs	89.8%	93.1%	0.631
SFCC1	27.7%	9.7%		b/tsDMARD	43.1%	38.9%	0.560
SFCC2	56.2%	62.5%		glucocorticoids	29.9%	44.4%	0.036
SFCC3	15.3%	26.4%					
SFCC4	0.7%	1.4%					

Notes: * DAS28 is calculated with 4 variables and CRP. Age, disease duration, ESR, PtGA, DAS28 are reported as mean (SD) and tested with 2-sided independent t tests, while CRP, TJC, SJC are reported as median (IQR) and teste with Mann Whitney tests. Nominal variables are reported as percentage of subgroup and are tested with χ^2 tests. Abbreviations: + positive; ACPA – anti-citrullinated protein antibodies; b/cs/tsDMARDs – biologic, conventional synthetic or targeted synthetic disease-modifying antirheumatic drugs; CRP – C-reactive protein; DAS28 – disease activity score with 28 joints; ESR – erythrocyte sedimentation rate; HDA – high disease activity; IQR – interquartile range; LDA – low disease activity; MDA – moderate disease activity; PHQ-9 – Patient Health

Questionnaire-9; PtGA – patient global assessment; RA – rheumatoid arthritis; RF – rheumatoid factor; SD – standard deviation; SFCC – Steinbrocker functional capacity class; SJC – swollen joint count; SRPC – Steinbrocker radiographic progression class; TJC – tender joint count; y – years.

Table 4. Comparison of RA variables according to HADS-D cutoff.

	HADS-D ≤10 (n=178)	HADS-D >10 (n=31)	p		HADS-D ≤10 (n=178)	HADS-D >10 (n=31)	p
women	91.6%	96.8%	0.315	CRP (mg/L)	4.6 (9.0)	5.6 (21.8)	0.119
age (y)	61.2 (11.6)	63.7 (11.0)	0.339	ESR (mm/h)	26.3 (22.5)	38.7 (22.9)	0.012
RA duration (y)	10.0 (8.4)	15.2 (13.1)	0.028	TJC	2 (6)	6 (6)	0.000
RF +	70.5%	74.2%	0.672	SJC	0 (3)	3 (5)	0.006
ACPA +	75.0%	83.9%	0.284	PtGA (mm)	40 (26)	57 (19)	0.001
RF, ACPA +	62.9%	74.2%	0.226	DAS28*	3.4 (1.4)	4.5 (1.3)	0.000
SRPC			0.004	DAS28 activity			0.003
SRPC1	27.0%	9.7%		remission	34.3%	6.5%	
SRPC2	46.1%	32.3%		LDA	18.5%	12.9%	
SRPC3	16.3%	29.0%		MDA	32.0%	48.4%	
SRPC4	10.7%	29.0%		HDA	15.2%	32.3%	
SFCC			0.000	≥ 1 csDMARDs	90.4%	93.5%	0.815
SFCC1	24.7%	3.2%		b/tsDMARD	39.9%	51.6%	0.222
SFCC2	60.1%	48.4%		glucocorticoids	33.7%	41.9%	0.375
SFCC3	14.6%	45.2%					
SFCC4	0.6%	3.2%					

Notes: * DAS28 is calculated with 4 variables and CRP. Age, disease duration, ESR, PtGA, DAS28 are reported as mean (SD) and tested with 2-sided independent t tests, while CRP, TJC, SJC are reported as median (IQR) and teste with Mann Whitney tests. Nominal variables are reported as percentage of subgroup and are tested with χ^2 tests. Abbreviations: + positive; ACPA – anti-citrullinated protein antibodies; b/cs/tsDMARDs – biologic, conventional synthetic or targeted synthetic disease-modifying antirheumatic drugs; CRP – C-reactive protein; DAS28 – disease activity score with 28 joints; ESR – erythrocyte sedimentation rate; HADS D – Hospital Anxiety and Depression Scale Depression; HDA – high disease activity; IQR – interquartile range; LDA – low disease activity; MDA – moderate disease activity; PtGA – patient global assessment; RA – rheumatoid arthritis; RF – rheumatoid factor; SD – standard deviation; SFCC – Steinbrocker functional capacity class; SJC – swollen joint count; SRPC – Steinbrocker radiographic progression class; TJC – tender joint count; y – years.

Table 5. Comparison of RA variables according to HADS-A cutoff.

	HADS-A ≤10 (n=141)	HADS-A >10 (n=68)	p		HADS-A ≤10 (n=141)	HADS-A >10 (n=68)	p
women	88.7%	100%	0.004	CRP (mg/L)	4.3 (8.5)	6.3 (11.7)	0.183
age (y)	61.0 (11.7)	62.8 (11.2)	0.289	ESR (mm/h)	26.6 (18.6)	31.4 (21.1)	0.085
RA duration (y)	10.3 (8.6)	11.9 (10.9)	0.157	TJC	2 (6)	4 (6)	0.025
RF +	70.5%	72.1%	0.817	SJC	0 (3)	1 (4)	0.216
ACPA +	75.5%	77.9%	0.703	PtGA (mm)	40 (26)	46 (24)	0.169
RF, ACPA +	63.1%	67.6%	0.521	DAS28*	3.4 (1.5)	3.8 (1.4)	0.130

SRPC			0.139	DAS28 activity	0.349		
SRPC1	28.4%	16.2%		remission	34.0%	22.1%	
SRPC2	44.0%	44.1%		LDA	16.3%	20.6%	
SRPC3	14.9%	25.0%		MDA	33.3%	36.8%	
SRPC4	12.8%	14.7%		HDA	16.3%	20.6%	
SFCC			0.015	≥ 1 csDMARDs	92.2%	88.2%	0.607
SFCC1	26.2%	11.8%		b/tsDMARD	41.1%	42.6%	0.835
SFCC2	57.4%	60.3%		glucocorticoids	31.9%	41.2%	0.188
SFCC3	16.3%	25.0%					
SFCC4	0	2.9%					

Notes: * DAS28 is calculated with 4 variables and CRP. Age, disease duration, ESR, PtGA, DAS28 are reported as mean (SD) and tested with 2-sided independent t tests, while CRP, TJC, SJC are reported as median (IQR) and teste with Mann Whitney tests. Nominal variables are reported as percentage of subgroup and are tested with χ^2 tests. Abbreviations: + positive; ACPA – anti-citrullinated protein antibodies; b/cs/tsDMARDs – biologic, conventional synthetic or targeted synthetic disease-modifying antirheumatic drugs; CRP – C-reactive protein; DAS28 – disease activity score with 28 joints; ESR – erythrocyte sedimentation rate; HADS A – Hospital Anxiety and Depression Scale Anxiety; HDA – high disease activity; IQR – interquartile range; LDA – low disease activity; MDA – moderate disease activity; PtGA – patient global assessment; RA – rheumatoid arthritis; RF – rheumatoid factor; SD – standard deviation; SFCC – Steinbrocker functional capacity class; SJC – swollen joint count; SRPC – Steinbrocker radiographic progression class; TJC – tender joint count; y – years.

Table 6. Questionnaire scores according to RA characteristics.

		PHQ9	HADS-D	HADS-A
sex	women	8.3 (4.9)	6.3 (4.0)	8.9 (4.5)
	men	5.2 (3.5)	5.6 (3.8)	5.5 (2.8)
	p	0.013	0.466	0.003
RF	negative	8.1 (4.3)	5.9 (3.7)	8.6 (4.0)
	positive	8.1 (5.1)	6.4 (4.1)	8.7 (4.6)
	p	0.973	0.419	0.888
ACPA	negative	7.6 (4.4)	5.9 (3.6)	8.5 (4.5)
	positive	8.2 (5.0)	6.4 (4.1)	8.7 (4.4)
	p	0.461	0.434	0.789
Steinbrocker radiographic stage	1	5 (5)	4 (4)	7 (6)
	2	8 (8)	6 (4)	9 (8)
	3	9 (6)	8 (7)	10 (7)
	4	7 (6)	8 (7)	8 (8)
	p	0.011	0.009	0.045
Steinbrocker functional stage	1	5 (5)	4 (5)	6 (6)
	2	7 (8)	6 (6)	9 (7)
	3	9 (7)	9 (6)	10 (8)
	4	11 (5)	9 (7)	17 (4)
	p	0.001	0.000	0.005
RA disease activity*	remission	6 (5)	4 (5)	7 (7)
	low	8 (9)	5 (5)	8 (8)
	moderate	8 (7)	6 (6)	9 (6)
	high	10 (9)	9 (6)	10 (6)
	p	0.000	0.000	0.058

b/tsDMARD	no	8.3 (4.8)	6.2 (3.8)	8.5 (4.3)
	yes	7.8 (4.9)	6.3 (4.2)	8.8 (4.6)
	p	0.339	0.929	0.619
glucocorticoids	no	7.8 (5.1)	5.8 (3.9)	8.2 (4.5)
	yes	8.6 (4.4)	6.2 (4.0)	9.4 (4.3)
	p	0.175	0.018	0.074

Notes: * According to DAS28 with 4 variables and CRP. Differences of PHQ9 and HADS were assessed with 2-sided independent t tests for sex, RF status, ACPA status, b/tsDMARD treatment and glucocorticoid treatment and are reported as mean (SD), and with Kruskal Wallis tests for SRS stages, SFR stages and RA activity classes and are reported as median (IQR). Abbreviations: ACPA – anti-citrullinated protein antibodies; b/tsDMARDs – biologic or targeted synthetic disease-modifying antirheumatic drugs; CRP – C-reactive protein; DAS28 – disease activity score with 28 joints; HADS D/A – Hospital Anxiety and Depression Scale Depression/Anxiety; IQR – interquartile range; PHQ-9 – Patient Health Questionnaire-9; RA – rheumatoid arthritis; RF – rheumatoid factor; SD – standard deviation.

4. Discussion

The likely depression and anxiety diagnoses screened with the self-reported questionnaires PHQ9 and HADS were higher than their known medical history of depression and anxiety. As previously discussed, the reported prevalence of depression and anxiety in RA patients has a significant variability because of the multiple thresholds of the questionnaires used in different studies. For example, when using the HADS measure, the range of estimates for depression was between 14.8% and 48% due to the use of variable cut-off scores. Screening for anxiety utilizing the HADS scale can generate a prevalence that varies from 14.8% to 48% [23].

When evaluating depression or anxiety prevalence in RA, all screening tools need clinical confirmation. Nevertheless, the high difference between the proportion of patients with confirmed diagnosis of depression and anxiety and the possible diagnoses after applying screening questionnaires should raise awareness over the fact that most RA patients with psychiatric disorders are left undiagnosed and untreated, which leads to poor long term outcomes.

It has been shown in multiple studies that the severity of depression correlates with RA disease activity and with long-term poor outcome [11]. Different observational studies revealed that high depression scores were associated with RA disease activity, without a clear confirmation of causality or direction [24]. A bidirectional relationship between depression and disease activity is possible, as studies in early RA reported that higher joint count and disease activity at baseline are associated with the presence and persistence of depression at 6 months [25]. A study by Fragoulis *et al* that evaluated depression and anxiety with the HADS found a significant correlation between the HADS scores for depression and anxiety and DAS28-CRP at 6 and 12 months [26]. Similar results were obtained by Matcham *et al.* in which persistent depressive and anxiety symptoms were associated with higher values of DAS28 [10]. A systematic review and meta-analysis by Machin *et al.* that included five studies mentioned a significant correlation between anxiety and increased DAS28 and decreased life quality [27]. The specialized literature has shown that depression leads to higher disease activity through association with the subjective components of the disease activity score (DAS28), such as tender joint count or patient global assessment [28]. Studies by Michelsen *et al.* or Matcham *et al.* found a correlation between the presence of depression and anxiety with higher TJC and higher VAS [29,30]. An additional study published by Matcham *et al.* observed that the presence of depression had a strong correlation with higher DAS28, higher tender joint count, but also higher swollen joint count [10]. Most of the studies suggest that anxiety is significantly associated with the more subjective components of disease activity such as pain levels, patient global assessments and tender joint count, without any correlations with the swollen joint count or acute phase reactants [27]. Objective measures, such as swollen joint counts [31] and inflammatory markers of disease activity

have been variably associated with baseline depression in different studies [26]. Some studies support the concept of a close relationship between inflammation and depression, as CRP levels were correlated with depression scores at subsequent follow-up time-points. Conversely, higher CRP levels at baseline have also been shown to distinguish between RA patients who would go on to develop depression [29]. Kekow et al. reported higher CRP levels at baseline in patients who had depression compared to those who did not [13]. Regarding the association between anxiety and CRP levels, there have not been any reported correlations.

Patients with depression also tend to have poor functional status, partly because of poor radiological outcomes in the presence of depression [32]. On the other hand, any improvement in depressive symptoms may lead to improvement in the functional status of the patient [26]. In a cohort of patients with RA and undifferentiated arthritis Kronisch et al. revealed that the baseline predictors of disability at 1 year are dominantly psychosocial and include high baseline disability, work disability, depression, anxiety and being overweight [33].

A prospective multicenter observational study by Michelsen et al. found that depression and anxiety were both negative predictors for RA remission after 3 and 6 months of treatment [29], while a pooled analysis of five randomized controlled trials observed that only comorbid depression and not anxiety was associated less frequently with remission [28].

In this study patients who screened positive for depression according to the utilized threshold (PHQ9 of 10 or more) had significantly higher disease activity class and DAS28, corresponding with the fact that depression correlates with RA disease activity [10]. As the specialized literature mentioned, this subgroup of patients also had higher values of the subjective components of disease activity, such as tender joint count and patient global assessment [27]. Additionally, swollen joint count also had high levels [31], which was also reported in other findings. The patients with a PHQ9 of 10 or more had worse functional stages and an increased frequency of glucocorticoid treatment use. Patients with a possible depression diagnosis utilizing HADS-D score of more than 10 presented almost similar characteristics with those with a PHQ9 of 10 or more with some notable differences. They shared higher number of tender and swollen joints, patient global assessment, DAS28, disease activity classes and functional stages, additionally, they had higher radiographical damage, higher levels of ESR and significantly higher mean disease duration. A prospective study done by Kwiatkowska et al. in 2018 identified disease duration as an important factor in the prevalence of depression [34]. Patients with a HADS-A score of more than 10 were more frequently women, women being more frequently affected by anxiety, and they had higher tender joint counts as other studies suggested [27] and significantly worse functional staging of RA. PHQ9, HADS-D and HADS-A scores were significantly higher in patients with more severe disease activity class, radiographic damage, functional stage. Additionally, PHQ9 and HADS-A had higher values in women and HADS-D scores were significantly higher in patients with glucocorticoid use.

The results of the current study should be interpreted taking into consideration the following limitations: cross-sectional design (which cannot establish causation or temporal relationships between RA and depression/anxiety); measurement bias of self-reported questionnaire data and possible local culture variations (underreporting symptoms caused by fear of stigmatization or patient-physician relationship influence); the diagnostic tool limitation (e.g., clinical interview versus standardized questionnaire); additional unaddressed confounding (such as fibromyalgia, chronic pain) and unmeasured variables (socioeconomic status, social support, coping mechanisms, and lifestyle factors); possible selection bias caused by recruitment from a specialized hospital.

5. Conclusions

Depression and anxiety are highly prevalent in the RA population and are associated with higher levels of pain, physical disability and disease activity. Most RA patients are underdiagnosed with depression and anxiety. These comorbid mental illnesses take an important toll on the overall quality of life of patients with RA. Taking into consideration the major impact of these psychiatric diseases on RA patients, it is highly important to screen patients on a routine basis, for early referral

to a psychiatry specialist for diagnosis and treatment, in hopes of improving disease activity and life quality of RA patients.

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Abbreviations

The following abbreviations are used in this manuscript:

RA	rheumatoid arthritis
HADS	Hospital Anxiety and Depression Scale
PHQ9	Patient Health Questionnaire
HADS-D	Hospital Anxiety and Depression Scale – Depression subscale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
DAS28	Disease Activity Score – 28 joints count
VAS	Visual analogue scale
ESR	Erythrocyte sedimentation rate
CRP	C reactive protein
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Diseases
IDD	Inventory to Diagnose Depression
CESD	Center for Epidemiological Studies Depression Scale
BDI	Beck Depression Inventory
GDS	Geriatric Depression Scale
cs/b/ts	conventional synthetics/ biologics / targeted synthetics Disease modifying
DMARD	antirheumatic drugs
ACPA	anti-citrullinated protein antibodies
TJC	Tender joint count
SJC	Swollen joint count
SRPC	Steinbrocker radiographic progression
SFCC	Steinbrocker functional capacity class
IQR	Interquartile range
SD	Standard deviation
PtGA	Patient global assesment

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