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# Depression is associated with increased disease activity and higher disability in a large Italian cohort of patients with rheumatoid arthritis

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## Abstract

**Introduction:** Depression is a quite common comorbidity in patients with rheumatoid arthritis (RA) and is thought to influence its severity. This study aims to estimate, in a large cohort of Italian patients with RA, the prevalence of depression and to investigate the clinical correlates of depression in terms of disease activity and disability.

**Methods:** This is a cross-sectional study enrolling 490 outpatients with RA (80% female, mean age 59.5). The Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of depression with a cut-off of 11. We collected data about disease activity and disability with DAS28, TJC-68, PhGA, PGA, VAS, DAS28, SDAI, CDAI and HAQ.

**Results:** Prevalence of depression was 14.3% (95% CI: 11–17%). Depressed patients, when compared with not depressed ones, were found to have higher scores for TJC-68 ( $p=0.011$ ), PhGA ( $p=0.001$ ), PGA ( $p=0.001$ ), VAS ( $p=0.001$ ), DAS28 ( $p=0.007$ ), SDAI ( $p=0.001$ ), CDAI ( $p=0.001$ ) and HAQ ( $p=0.001$ ). Out of the 70 depressed patients, 30 subjects, already known to be depressed in the past, were still depressed at the time of the assessment, with only 11 (15.7%) under antidepressants. A multivariate analysis showed that male sex, higher PGA score, use of antidepressants and higher HAQ score were significantly associated with an increased risk of depression.

**Conclusions:** Our study shows that depression is common in RA and may affect its activity mainly via an alteration in the perception of the disease. Although its important implications, depression is still under-diagnosed and its management is inadequate.

**Keywords:** Depression, Rheumatoid arthritis, Disease activity, Disability

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a prevalence of 0.5–1% in Europe, with the lower values in southern countries [1]. It primarily involves peripheral joints, damaging cartilages and

bones, and leads progressively to disability. RA shows also systemic manifestations and it has been associated to systemic comorbidities, as depressive and anxiety disorders [2].

In patients with RA, the prevalence of depression ranges between 14.8 and 22.5%, which is two to three times higher than in the general population [3], reaching a 47% lifetime risk [4, 5]. In addition, about 39% of patients affected by RA have also sub-threshold depressive symptoms [5]. Finally, depression occurs twice as

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often in females with RA as compared to males suffering from RA [6].

The presence of depression has been associated with increased pain perception [4], increased level of physical disability [7], enhanced health care costs [6], and greater mortality [4]. Notably, it has been demonstrated a significant association between persistent depression and high continuous disease activity, measured by the Clinical Disease Activity Index (CDAI) [8]. Notably, most of the activity scores commonly used in rheumatology are based also on subjective measures that may be affected by the psychological status [9] and may further influence the assessment of disease activity.

Finally, depression was found to be a strong negative predictor of remission [10], thus should be evaluated in every patient in order to increase the probability of a good disease control.

Since there is a possibly bidirectional relationship between the severity of both rheumatic disease and depressive disorders, it is fundamental to study the clinical correlates of depression in RA patients in order to improve the clinical outcome of RA.

The present study aims (1) to estimate, in a large sample of Italian patients affected by Rheumatoid Arthritis, the prevalence of depressive disorders; and (2) to investigate the clinical correlates of depression in terms of RA disease activity and disability. Specifically, we hypothesized that RA individuals affected by depression were characterized by higher levels of RA disease activity and disability when compared to non-depressed ones. The present study offers the opportunity to increase our knowledge on the comorbidity by investigating depression and its clinical correlates, as part of the routine clinical monitoring, in a large real life RA sample from a real-world outpatient setting. Studying the clinical correlates of depression in RA is a relevant issue in order to define appropriate screening and treatment programs to prevent worse outcome for both depression and RA.

## Material and methods

This is an observational, cross-sectional study examining the clinical correlates of depressive disorders in a cohort of patients affected by Rheumatoid Arthritis on DMARDs treatment for at least one year. Individuals followed at the Unit of Rheumatology, University Hospital of Verona, Italy, in the period between March 2016 and February 2017 were enrolled during a routine outpatient visit. The inclusion criteria were: (1) age  $\geq 18$  years; (2) RA diagnosis according to the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) 2010 [11]. Individuals with fibromyalgia, connective tissue diseases (LES, Sjogren, scleroderma, dermatomyositis, polymyositis), vasculitis, gout, infective

arthritis, rheumatic polymyalgia or other severe systemic diseases were excluded.

A comprehensive set of standardized instruments was used to collect socio-demographic and clinical information.

Specifically, RA-related characteristics including disease duration, 28 tender/swollen joints count (TJC 28/SJC 28) [12], 68 tender/swollen joints count (TJC 68/SJC 68), Visual Analogue Scale (VAS, 0–100 mm) for joint pain, Physician Global Assessment (PhGA, 0–10) and Patient Global Assessment (PGA, 0–10), were collected. RA disease activity and disability were assessed with 28-joints Disease Activity Score (DAS28) [1], Simplified Disease Activity Index (SDAI) [1], Clinical Disease Activity Index (CDAI) [1] and Health Assessment Questionnaires (HAQ) [13]. Patients were assessed for the presence of any comorbidity and for smoking. Data about current rheumatic medications, antidepressants or benzodiazepines were recorded. Body Mass Index (BMI,  $\text{kg}/\text{m}^2$ ) was calculated as following: weight was measured without shoes, and in light indoor clothes, using a balance beam scale; height was measured without shoes using a fixed stadiometer.

Blood samples were collected to detect the presence of anti-citrullinated protein antibody (ACPA) and/or rheumatoid factor (RF), erythrocyte sedimentation rate (ESR, mm/hour), C-reactive protein (CRP; mg/L), vitamin D level (25-OH-D3, nmol/L).

Depressive and anxious symptomatology was assessed using the Hospital Anxiety and Depression Scale (HADS) [8]. The HADS is a self-administered instrument validated in a hospital setting and developed for evaluating depression in somatic primary or secondary care [9]. It is composed by two subscales, one for depression (HADS-D) and one for anxiety (HADS-A), each constituted by seven items. Every item is scored from 0 to 3, and higher scores indicate more severe symptoms. Total sum score ranges from 0 to 21 for HADS-D. For the present study, we decided to use only the HADS-D with a cut-off of 11, allowing us to identify with greater specificity depressed subjects.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki [14].

## Statistical analyses

Descriptives were given for all variables. Comparisons between depressed patients (HADS-D score  $\geq 11$ ) and not depressed patients (HADS-D score  $< 11$ ) were assessed by Chi-square tests for categorical variables and t-tests (2 independent groups) for continuous variables. Each socio-demographic and clinical variable which resulted significantly different in the two groups was entered into a univariable linear regression model with HADS-D score as the dependent variable. Subsequently,

only those variables associated at  $p < 0.10$  entered into a series of multivariable hierarchical linear regression models (model 1: demographics; model 2: plus RA-related variables; model 3: plus RA therapy; model 4: plus psychotropic therapy; model 5: plus RA disease activity and disability indices). The R-square change at each step was used to determine the variance explained by each set of variables. Collinearity among the independent variables was explored by calculating the individual variance inflation factors. In the final model, these values ranged between 1.10 and 3.29, thus indicating the absence of multicollinearity. All tests were 2-tailed. Statistical analyses were performed using SPSS 22 for Windows.

## Results

### Prevalence of depression and its association with socio-demographic characteristics

We assessed 490 patients with RA (80% female, with mean age of about 60 years). We found that the prevalence of depression was 14.3% (95% CI: 11–17%). Indeed, out of the 490 participants, 70 patients scored  $\geq 11$  in HADS-D questionnaire (Table 1). Depression was more frequent in females and in unemployed patients ( $p = 0.001$  and  $p = 0.034$ , respectively). No other socio-demographic characteristics were associated with depression.

### The association between depression and clinical characteristics

We found that out of 70 depressed patients, 30 (42.9%) reported a personal history of depression. Moreover, patients with depression, when compared to non-depressed ones, have higher TJC68 ( $p = 0.011$ ),

PhGA ( $p < 0.011$ ), PGA ( $p < 0.011$ ) and VAS ( $p < 0.011$ ) (Table 2). There were no differences between the two groups in terms of duration of illness, RF and/or ACPA seropositive form, number of erosions, family history of rheumatic disease, TJC28, SJC28, SJC66 and biological characteristics.

Most patients (90.8%) presented at least one comorbidity, with the cardiovascular the most represented one (56.1%) (Table 3). Regarding comorbidity, there were no differences between the two groups.

By considering medications (Table 4), almost half of the cohort (49.4%) used steroids, with a difference between depressed (60.0%) and not depressed (47.6%) patients ( $p = 0.050$ ). One hundred and four patients (21.2%) used to take NSAIDs for ten or more days per month, with a significant difference between depressed (32.9%) and not depressed (19.3%) patients ( $p = 0.010$ ).

There were no differences between the two groups in terms of cDMARDs and biologics' use. Out of the 70 depressed patients, 11 (15.7%) were under antidepressant treatment given a personal history of depression. On the other hand, a significantly lower proportion of non-depressed patients has had a previous diagnosis of depression and were taking anti-depressant drugs at the moment of assessment (4.5%,  $p < 0.001$ ). Finally, depressed patients were found to take a higher number of drugs, i.e. anti-rheumatic drugs plus psychotropic therapy (6.4 versus 5.0,  $p < 0.001$ ).

### The association between depression and RA activity and disability

Depressed and not depressed patients were compared on RA activity and disability (Table 5) by means of

**Table 1** Socio-demographic characteristics of RA patients and their association with depression (n = 490)

Socio-demographics	Total sample (n = 490)	Depression according to HADS-D (cut-off $\geq 11$ )		p-value (Chi-square or t test)
		Not depressed (n = 420)	Depressed (n = 70)	
Age (years), mean (sd)	59.5 (12.2)	59.2 (12.1)	61.5 (12.9)	0.141
Female, n (%)	392 (80.0%)	326 (77.6%)	66 (94.3%)	0.001
Marital status, n (%)				
Unmarried	57 (11.6%)	48 (11.5%)	9 (12.9%)	0.190
Married	355 (72.4%)	311 (74.0%)	44 (62.8%)	
Widowed	38 (7.8%)	30 (7.1%)	8 (11.4%)	
Divorced	40 (8.2%)	31 (7.4%)	9 (12.9%)	
With children, n (%)	395 (80.6%)	339 (80.7%)	56 (80.0%)	0.889
Low education, n (%)	299 (61.0%)	253 (60.2%)	46 (65.7%)	0.428
Occupation, n (%)				
Employed	192 (39.2%)	173 (41.2%)	19 (27.1%)	0.034
Unemployed	298 (60.8%)	247 (58.8%)	51 (72.9%)	

Low education: primary/secondary school

**Table 2** Clinical characteristics and their association with depression (n = 490)

Clinical characteristics	Total sample (n = 490)	Depression according to HADS-D (cut-off $\geq 11$ )		p-value (Chi-square or t test)
		Not depressed (n = 420)	Depressed (n = 70)	
Positive personal history for depression, n (%)	106 (21.6%)	76 (18.1%)	30 (42.8%)	<0.001
RF and/or ACPA positive, n (%)	292 (59.6%)	246 (58.6%)	46 (65.7%)	0.294
BMI (kg/m <sup>2</sup> ), mean (sd)	25.7 (4.8)	25.7 (4.8)	26.0 (5.1)	0.606
Smoker, n (%)	64 (13.1%)	57 (13.6%)	7 (10.0%)	0.565
Positive family history for rheumatologic disease, n (%)	127 (25.9%)	104 (24.8%)	23 (32.8%)	0.184
Erosions, n (%)	212 (43.3%)	179 (42.6%)	33 (47.1%)	0.516
Disease duration (years), mean (sd)	12.5 (9.6)	12.5 (9.6)	12.4 (9.5)	0.931
TJC 28, mean (sd)	2.1 (3.5)	2.0 (3.5)	2.6 (3.9)	0.197
SJC 28, mean (sd)	1.1 (2.2)	1.1 (2.3)	1.2 (2.1)	0.647
TJC 68, mean (sd)	2.6 (4.0)	2.4 (3.8)	3.7 (4.9)	0.011
SJC 66, mean (sd)	1.4 (2.7)	1.4 (2.7)	1.7 (2.4)	0.324
PhGA, mean (sd)	4.4 (2.7)	4.2 (2.7)	5.5 (2.5)	<0.001
PGA, mean (sd)	5.3 (2.4)	5.1 (2.4)	6.6 (2.2)	<0.001
VAS pain, mean (sd)	5.0 (2.7)	4.8 (2.7)	6.3 (2.2)	<0.001
ESR, mean (sd)	19.9 (16.6)	19.6 (16.6)	21.9 (16.2)	0.276
CRP, mean (sd)	5.6 (8.8)	5.8 (9.3)	4.2 (4.3)	0.179
Vitamin D, mean (sd)	68.8 (28.3)	69.0 (28.1)	68.1 (30.0)	0.806
Haemoglobin, mean (sd)	13.4 (1.3)	13.4 (1.3)	13.2 (1.3)	0.105

RF rheumatoid factor; ACPA anti-citrullinated protein antibodies; BMI Body Mass Index, TJC tender joint count; SJC swollen joint count; PhGA physician global assessment; PGA patient global assessment; VAS visual analogue scale; ESR erythrocyte sedimentation rate; CRP C-reactive protein

**Table 3** Presence of comorbidities and their association with depression (n = 490)

Comorbidities	Total sample (n = 490)	Depression according to HADS-D (cut-off $\geq 11$ )		p-value (Chi-square or t test)
		Not depressed (n = 420)	Depressed (n = 70)	
Comorbidities, n (%)	445 (90.8%)	379 (90.2%)	66 (94.3%)	0.373
Cardiovascular	275 (56.1%)	231 (55.0%)	44 (62.9%)	0.243
Endocrinological	127 (25.9%)	105 (25.0%)	22 (31.4%)	0.302
Neoplastic	58 (11.8%)	49 (11.7%)	9 (12.9%)	0.841
Pulmonary	43 (8.8%)	36 (8.6%)	7 (10.0%)	0.651
Neurological	9 (1.8%)	8 (1.9%)	1 (1.4%)	0.999
Gastroenterological	144 (29.4%)	117 (27.9%)	27 (38.6%)	0.088
Rheumatological	218 (44.5%)	177 (42.1%)	41 (58.6%)	0.013

DAS28-CRP, SDAI, CDAI and HAQ scores and their categories of activity/disability (remission, low, moderate, high).

Depressed patients scored significantly higher on all RA activity and disability scores. Moreover, by considering the categories of DAS28-CRP, SDAI and CDAI, the percentage of depressed patients increases from remission to moderate disease activity group, where it reaches its maximum, while decreases in high disease activity group. On the contrary, the trend between depression and disability shows that depression became more

frequent in subjects with severe and very severe disability according to HAQ scores ( $p = 0.001$ ).

A series of univariable linear regression models with HADS-D score as the dependent variable and each of the variables pertaining to conceptual blocks (demographics, RA-related variables, RA therapy, psychotropic therapy, disease activity and disability indices) as the independent one was estimated. Those variables which resulted associated at  $p < 0.10$  with the HADS-D score were entered into multivariable linear regression models, beginning from demographics and adding variables from the other

**Table 4** Association between anti-rheumatic and psychotropic therapy and depression (n = 490)

Therapy	Total sample (n = 490)	Depression according to HADS-D (cut-off $\geq 11$ )		p-value (Chi-square or t test)
		Not depressed (n = 420)	Depressed (n = 70)	
<i>RA therapy</i>				
Corticosteroids, n (%)	242 (49.4%)	200 (47.6%)	42 (60.0%)	0.050
NSAIDs (> 10 per month), n (%)	104 (21.2%)	81 (19.3%)	23 (32.9%)	0.010
Vitamin D, n (%)	388 (79.2%)	328 (78.1%)	60 (85.7%)	0.146
<i>Anti-rheumatic drugs</i>				
Only cDMARDs, n (%)	199 (40.6%)	170 (40.5%)	29 (41.4%)	0.937
Only anti-TNF $\alpha$ , n (%)	67 (13.7%)	57 (13.6%)	10 (14.3%)	
cDMARDs plus anti-TNF $\alpha$ , n (%)	105 (21.4%)	92 (21.9%)	13 (18.6%)	
No cDMARDs, no anti-TNF $\alpha$ , n (%)	119 (24.3%)	101 (24.0%)	18 (25.7%)	
<i>Psychotropic therapy</i>				
Antidepressants, n (%)	30 (35.9%)	19 (4.5%)	11 (15.7%)	<0.001
Total number of drugs, mean (sd)	5.2 (2.5)	5.0 (2.4)	6.4 (2.8)	<0.001

cDMARDs: conventional disease-modifying antirheumatic drugs; anti-TNF $\alpha$ : anti-tumor necrosis factors drugs; Total number of drugs: anti-rheumatic drugs plus psychotropic therapy

conceptual blocks (Table 6). Males (model 1) have lower levels of depression than females (variance explained 3.3%); addition of RA-related variables (model 2) raised the variance explained up to 10.7%, with PGA score significantly associated with higher depression levels. Corticosteroids and NSAIDs (model 3) were not associated with depression score, while the use of antidepressants and the total number of assumed drugs (model 4) increased the variance by 2.2%, with both variables being significantly associated with higher depression levels. Finally, when disease activity and disability indices (SDAI and HAQ, respectively) were added (model 5), the model explained 14.5% of the variance, with higher HAQ being associated with higher depression score. At this step, however, the total number of assumed drugs was no longer statistically significant.

## Discussion

This study evaluates the prevalence of depression and its clinical correlates in terms of disease activity and disability in a large sample of patients affected by RA. We found a prevalence of depression equal to 14.3% (95% CI: 11–17%), that is almost three times higher than the prevalence in the general population [15]. Depression should therefore be considered such as one of the commonest comorbidities of RA and it should always be evaluated with screening tests, and treated whether necessary, to improve clinical outcomes [16]. We also found that depressed patients had higher disease activity and increased disability indices (SDAI and HAQ, respectively). This result underlines the importance of distinguishing between an increased illness

activity and an altered disease perception secondary to depression.

Previous studies showed great variability in the prevalence of depression in patients suffering from RA, reaching up to 34–48% [10, 12]. This variability may be explained by the different instruments and heterogeneity in criteria used to diagnose depression [17]. To avoid an overestimation of depression, we decided to use HADS-D with a cut-off of 11, allowing to identify with greater specificity depressed subjects, since it excludes elements that may reflect physical rather than psychological problems. Specifically, the HADS-D does not contain questions that investigate quality of sleep, fatigue and appetite, symptoms that are common in both depression and RA, as it happens in other questionnaires as Hamilton Rating Scale for Depression (HAM-D) [18]. Regarding the choice of the cut off for the HADS, a previous study [19] used a cut-off  $\geq 8$ , thus including patients with borderline depression leading to a risk to overestimate the prevalence of depression. A systematic review [13] has identified 30 studies in RA patients in which HADS-D with a cut-off  $\geq 11$  was used; an average prevalence of depression of 14.8% emerged, which is very close to our result.

Regarding the socio-demographic correlates of depression, we found a significantly higher prevalence of depression among female patients (16.8%) compared to males (4.1%), in line with previous studies [14, 20, 21]. This evidence may be explained by the higher prevalence of depression in the general population among women [15]. In addition, women tend to undergo more frequently medical treatment, thus increasing the likelihood

**Table 5** Association between RA activity/disability and depression (n = 490)

Disease activity and disability indices	Total sample (n = 490)	Depression according to HADS-D (cut-off $\geq 11$ )		p-value (Chi-square or t test)
		Not depressed (n = 420)	Depressed (n = 70)	
<i>DAS28-CRP, mean (sd)</i>	2.9 (1.1)	2.8 (1.1)	3.2 (0.9)	0.007
<i>DAS28-CRP, n (%)</i>				
Remission	231 (47.1%)	209 (49.7%)	22 (31.4%)	0.008
Low	82 (16.7%)	71 (16.9%)	11 (15.8%)	
Moderate	160 (32.7%)	125 (29.8%)	35 (50.0%)	
High	17 (3.5%)	15 (3.6%)	2 (2.8%)	
<i>SDAI, mean (sd)</i>	13.4 (8.2)	12.9 (8.2)	16.3 (7.5)	0.001
<i>SDAI, n (%)</i>				
Remission	34 (6.9%)	32 (7.6%)	2 (2.8%)	0.001
Low	176 (35.9%)	163 (38.8%)	13 (18.6%)	
Moderate	243 (49.6%)	193 (46.0%)	50 (71.4%)	
High	37 (7.6%)	32 (7.6%)	5 (7.1%)	
<i>CDAI, mean (sd)</i>	12.9 (8.0)	12.3 (8.0)	15.9 (7.4)	0.001
<i>CDAI, n (%)</i>				
Remission	32 (6.5%)	30 (7.1%)	2 (2.8%)	0.001
Low	184 (37.6%)	171 (40.8%)	13 (18.6%)	
Moderate	223 (45.5%)	177 (42.1%)	46 (65.7%)	
High	51 (10.4%)	42 (10.0%)	9 (12.9%)	
<i>HAQ, mean (sd)</i>	0.8 (0.7)	0.7 (0.7)	1.2 (0.7)	<0.001
<i>HAQ, n (%)</i>				
Mild	133 (27.1%)	125 (29.8%)	8 (11.4%)	<0.001
Moderate	220 (44.9%)	193 (46.0%)	27 (38.6%)	
Severe	109 (22.2%)	84 (20.0%)	25 (35.7%)	
Very severe	28 (5.7%)	18 (4.2%)	10 (14.3%)	

DAS28 28-joint Disease Activity Score; SDAI Simplified Disease Activity Index; CDAI Clinical Disease Activity Index; HAQ Health Assessment Questionnaires

DAS28-CRP: remission if  $\leq 2.19$ , low if between 2.19 and 2.60, moderate if between 2.60 and 4.07, high if  $> 4.07$

SDAI: remission if  $\leq 3.3$ , low if between 3.3 and 11, moderate if between 11 and 26, high if  $> 26$

CDAI: remission if  $\leq 2.8$ , low if between 2.8 and 10, moderate if between 10 and 22, high if  $> 22$

HAQ: mild disability if  $\leq 0.1$ , moderate disability if between 0.1 and 1, severe disability if between 1 and 2, very severe disability if  $> 2$

of detecting depression [22]. Furthermore, men tend not to complain about their psychological disturbances; on the contrary women express themselves more emotionally, obtaining higher scores in questionnaires [23]. In our cohort, the percentage of depressed patients is significantly higher in those without an occupation (17.1%) than in workers (9.9%). Our results are in line with previous studies [26], suggesting that the employment status is protective against the development of depression in RA. An association between lower income and depression has also been detected [26]: less economic resources may reduce attention and spending for health. On the contrary, other studies reported a positive correlation between employment and depressive symptoms [24]. We have not distinguished retired from unemployed subjects, therefore, at least half of this group is composed by old retired people (i.e. unemployed and aged  $\geq 65$  years),

who could have negative feelings of worthlessness, fear of the future and sense of isolation, which are psychological feelings leading to the development of depressive symptoms [27]. Conversely, RA itself, causing disability, makes more difficult to find or keep a job, especially if it is a manual one.

On the other hand, 30 patients with a previous diagnosis of depression were still depressed at the time of the assessment. Out of them, 11 were depressed although under antidepressants. The remaining 19 depressed subjects were not diagnosed or treated despite a previous history of depression. A positive history for depression should be considered a risk factor for the persistence or recurrence of depression in RA. Moreover, we found that a considerable portion of patients (n = 40) with undetected depression had a negative history of depression. Thus, this under-recognized

**Table 6** Multivariable hierarchical linear regression models with HADS-D score as dependent variable (n = 490)

Independent variables	Dependent variable: HADS-D score Beta coefficients (p-value)				
	Model 1	Model 2	Model 3	Model 4	Model 5
<i>Socio-demographics</i>					
Being male	- 1.85 (<0.001)	- 1.42 (0.001)	- 1.41 (0.001)	- 1.41 (0.001)	- 1.18 (0.007)
<i>RA-related variables</i>					
PhGA		0.42 (<0.001)	0.40 (<0.001)	0.35 (<0.001)	0.29 (0.002)
PGA		0.06 (0.387)	0.05 (0.488)	0.04 (0.582)	0.05 (0.587)
<i>RA therapy</i>					
Corticosteroids			0.21 (0.547)	- 0.16 (0.657)	- 0.32 (0.383)
NSAIDs (> 10 per month)			0.55 (0.196)	0.48 (0.254)	0.37 (0.382)
<i>Antidepressants</i>					
Total number of drugs				0.16 (0.035)	0.10 (0.180)
<i>Disease activity and disability indices</i>					
SDAI					- 0.03 (0.422)
HAQ					0.97 (0.002)
<i>Goodness of fit indices</i>					
Adj R-squared %	3.3%	10.7%	10.7%	12.9%	14.5%
AIC	2723.9	2686.9	2688.9	2678.3	2671.4
BIC	2732.3	2703.7	2714.1	2711.9	2713.4
LR Chi2	-	41.0	1.9	14.6	10.9
p > Chi2	-	<0.001	0.379	<0.001	0.004

depression should be addressed with an appropriate screening and treatment, keeping in mind that even among patients who were under antidepressants, 34.1% were still depressed according to HADS-D, suggesting that in almost one third of cases those drugs are ineffective or maybe at inadequate dosage. These patients should be evaluated by a psychiatrist to optimize their therapy and followed up closely by the rheumatologist.

Considering the variables used to determine indices of disease activity, in our study there is a significant relationship between depression and TJC, PGA, PhGA and VAS, while no association was found between depression and disease duration, seropositivity, erosions, markers of inflammation, or swollen joints. Our data further support the association between depression and higher pain perception that may affect mainly subjective measurements, such as tender joints count, PGA and VAS, as reported [25, 26]. Notably, it has been calculated that each extra point of depression measured with HADS results in an increase of 0.59 in TJC and 2.07 in the PGA score [28]. Even if clinical measures based on patients' reports could have important limitations, since they can reflect the subjective perception of illness, influenced by many factors (beliefs, culture, mood), some studies have suggested that those measures are better in terms of prediction of long-term outcomes, compared to objective parameters [29]. Indeed, we observed that objective measurements

of disease activity (disease duration, ESR, CRP and SJC) were not associated with depressive symptoms, as reported in other studies [7, 18, 27, 30, 31], but in contrast with other ones [12, 17], in which objective scores affected mood.

Secondly, we found a significant association between RA disease activity and depression and between disability and depression, assessed through DAS28, SDAI, CDAI and HAQ, respectively. These findings were in line with previous studies [7, 12, 20]. Patients who experience a more active form of RA, with greater pain and inflammation, are at higher risk of developing depressive disorders. On the other hand, the presence of depression in individuals with a chronic disease such as RA may increase inflammation and reduce the pain threshold, making the disease more active and less prone to remission, compared to patients without mental disorders [19–21]. Our results underline that HAQ is the index that best correlates with depression, suggesting that physical disability deeply influence mental wellbeing. When we correlated depression with DAS28, CDAI and SDAI indices/scores we found, against our expectations, a greater prevalence of depressive disorders among patients with moderate disease activity compared to high disease activity. A possible explanation could be that patients with a very active disease are more frequently examined by

a rheumatologist, accordingly to the treat-to-target management [32], and this carefulness may potentially reduce depression. Therefore, moderate disease activity could be the category at the highest risk of developing depression, pointing to the importance of screening and monitoring depression in these patients.

The hypothesis that depressive symptoms in patients with RA may worsen pain and lead to greater assumption of analgesics is further confirmed by our evidence that patients treated with NSAIDs had higher prevalence of depression. It is worth mentioning that NSAIDs use is usually self-prescribed, linked to the patient's perception of their health status rather than being a treatment prescribed by the physician on the basis of objective measures. In our study, we found no significant association between the use of specific anti-rheumatic drugs and depressive disorders. On the other hand, one should keep in mind that it is also possible that patients with a more active RA may have an increased risk of depression [8], so the relationship between RA and depression could be bidirectional.

Depressive symptoms are also associated with physician perception of disease severity and may influence the way patients communicate pain and affecting clinician's empathy. Depressive symptoms could also overlap with some symptoms of RA, simulating a more active and severe arthritis. Furthermore, depression may create resistance or non-adherence to treatment [33] and this may require a greater therapeutic and patient-management effort.

This paper has several strengths. To our best knowledge, this is the first large study performed in Italy analyzing data from a large sample of patients (N=490) affected by RA. We recruited all subjects within the routine clinical practice, rather than a sample recruited with strict selection criteria, during a whole year in order to increment the generalizability of our results. We used a set of standardized questionnaires, covering a broad number of potential correlates of depression in RA, with special attention to disease activities and disability. Finally, this study arises from a strict collaboration between rheumatologist and psychiatrist leading to a multidisciplinary approach to such a relevant RA comorbidity, in both design and analysis of this paper.

The main limitation is the cross-sectional design of the study that cannot allow us to draw causal inferences on the relationship between depression and RA. Moreover, although we used the HADS, which is a well-validated and reliable screening tool, the diagnosis of depression was not confirmed by a psychiatrist.

## Conclusions

In conclusion, our study shows that depression is common in RA and can lead to an alteration in the perception of the disease since the presence of depression is associated with higher disease activity, pain perception, physical disability. This suggests the importance for the rheumatologist to screen and monitor depression in patients affected by RA in order to treat them appropriately. In addition, recognizing and treating depression may increase treatment adherence, further improving disease control. Although it could sound obvious, one should not forget that treating depression has significant positive effects on patients' well-being that is one of the main target of the rheumatologist work. Finally, since depression is still under-diagnosed and almost one third of the patients treated with antidepressants does not benefit from the treatment, a close collaboration between rheumatologists and psychiatrists is desirable for an adequate diagnosis and appropriate therapy.

## Abbreviations

25-OH-D3: Vitamin D; ACPA: Anti-citrullinated protein antibody; BMI: Body Mass Index; CDAL: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: 28-Joints Disease Activity Score; HADS-A: Hospital Anxiety and Depression Scale anxiety; HADS-D: Hospital Anxiety and Depression Scale depression; HAQ: Health Assessment Questionnaires Disability Index; PGA: Patient Global Assessment; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SDAI: Simplified Disease Activity Index; SJC: Swollen joints count; TJC: Swollen joints count; VAS: Visual Analogue Scale.

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## Authors' contributions

All authors read and approved the final manuscript and have had substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work.

## Availability of data and material

Data are available by direct request to the corresponding author.

## Declarations

### Ethics approval

The study protocol was approved by the local ethic committee (protocol number 15840, 30 March 2016).

### Consent to participate

Written informed consent was obtained after the nature of the study had been fully explained.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.



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